Improvement of hand and finger function in systemic sclerosis: game-based intervention informed by a 3D assessment of hand mobility

Kirstin Elena Eusterwiemann

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Abstract

Systemic sclerosis (SSc) is a rare rheumatic autoimmune disease, resulting in increased collagen production, leading to increased thickness and stiffness of the skin and reduced hand function. The hands are a critical contributor to the ability to perform activities of daily living (ADL), which is limited in patients with SSc. Therefore hand function is commonly assessed in clinics using patient-reported outcome measures (PROMs) or single distance measures during static finger flexion. In this thesis a three-dimensional motion analysis was conducted to assess the magnitude of impairment throughout functional tasks, as well as joint specific contributions to overall impairment. Study one showed that patients have significant movement impairment throughout the entire movement phase of functional tasks. Further impairments were found in all joints and movement directions, with no joint being more impaired than others.

The information was then used to inform a novel rehabilitation programme. Conventional programmes focus predominantly on flexion ability and patients show low adherence rates. A portable virtual rehabilitation (VR) tool was developed for the gamification of hand exercises allowing training of both flexion-extension as well as abduction-adduction ranges. The third study, a randomised-controlled trial, evaluated the effect of exercises on the VR tool compared to physiotherapy. Ability to perform ADLs was not significantly improved after exercises. Finger dexterity and mobility were significantly improved in both groups, whereby the VR group showed greater improvement across all assessed outcome measured compared to physiotherapy. Further, patients in the VR group showed higher levels of motivation and likelihood of adherence to the exercises in the future.

Overall the findings in this thesis highlighted that finger joint movement impairments are present in all joints and movement directions, as well as the suitability of virtual rehabilitation to improve or maintain hand function in patients with systemic sclerosis.

Research outputs and publications

Eusterwiemann, E., Robinson, M. A., Anderson, M., Barton, G.J. Is that a Vicon in your pocket? *Clinical Movement Analysis Society of the UK and Ireland Annual Meeting*, Salford, 6-7th April 2017. – Published abstract of an oral presentation. Won - Best Student Paper Award.

Eusterwiemann, E., Anderson, M., Robinson M. A., Barton G.J. Development of a Virtual Rehabilitation game for Scleroderma: Gender differences in unimpaired controls. *Rheumatology*. 56(2). Birmingham, 25-27th April 2017. – Published abstract of an oral presentation.

Eusterwiemann, E., Robinson, M. A., Anderson, M., Barton, G.J. Motion capture without markers using the Leap Motion Controller and artificial neural networks. *Gait & Posture*. 65. 2018. pp7-8. – Published abstract of an oral presentation. Won - Best Audience Paper Award.

Eusterwiemann, E., Robinson, M.A., Anderson, M., Barton, G.J. (2018) Motion capture without markers using the leap motion sensor and artificial neural networks. *Liverpool John Moores University – Faculty of Sciences*. Liverpool, 18th June 2018.

Eusterwiemann, E., Robinson, M.A., Anderson, M., Barton, G.J. (2018) Improved accuracy of markerless finger tracking with the Leap Motion, using an artificial neural network. *3D Analysis of Human Movement Symposium*. Salford, 2nd – 6th July 2018. – Published abstract of an oral presentation.

Eusterwiemann, E ., Robinson, M.A., Anderson, M., Barton, G.J. (2019) Quantifying hand movement limitations in scleroderma during functional tasks using the Movement Deviation Profile. International Society of Biomechanics Annual Conference, Calgary, 31st July – 4th August 2019. – Published abstract of an oral presentation.

Eusterwiemann, E., Robinson, M.A., Anderson, M., Barton, G.J. (2019) Comparing the effectiveness of virtual rehabilitation and physiotherapy on finger mobility in scleroderma patients. European Society for Movement Analysis in Adults and Children Annual Conference, Amsterdam, 23rd-28th September 2019. – Published abstract of an oral presentation.

Eusterwiemann, E., Anderson, M., Robinson, M.A., Barton, G.J. (2019) 'If You Don't Use It, You Lose It': Rehabilitation of Finger Dexterity and Ability to Perform Activities of Daily Living in Systemic Sclerosis. [abstract]. Arthritis Rheumatol. 71(10). – Published abstract of an poster presentation.

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List of Abbreviations

3D	Three-dimensional
AA	Abduction-adduction
ACA	Anti-centromere autoantibody
ADL	Activities of Daily Living
ANA	Anti-nuclear autoantibody
AoR	Axis of rotation
ATA	Anti-topoisomerase Scl-70 autoantibody
CHFS	Cochin Hand Function Scale
CHFS-6	Cochin Hand Function Scale – 6 – Shortform
CMC	Carpometacarpal
CoR	Centre of rotation
DASH	Disabilities of the Arm, Shoulder and Hand Test
dFTP	delta-Finger-to-Palm index
DoF	Degree of freedom
dSSc	Diffuse Systemic Sclerosis
ECM	Extracellular matrix
EDAQ	Evaluation of Daily Activity Questionnaire
FE	Flexion-extension
FTP	Finger-to-Palm Index
HAMIS	Hand Mobility in Scleroderma
IC	Intercarpal
IP	Interphalangeal
JHFT	Jebsen Hand Function test
lcSSc	Limited cutaneous Systemic Sclerosis
LM	Leap Motion controller
lSSc	limited Systemic Sclerosis
MCP	Metacarpophalangeal
MDP	Movement Deviation Profile
MDP_{mean}	Mean Movement Deviation Profile
MEA_{mean}	Mean maximum extension angle

MHQ	Michigan Hand Questionnaire
mRSS	modified Rodnan Skin Score
NN	Neural network
PMC	Primary Motor Cortex
PROM	Patient-reported outcome measure
RA	Rheumatoid Arthritis
ROM	Range of motion
SHAQ	Scleroderma Health Assessment Questionnaire
SHFT	Sollerman Hand Function Test
SSc	Systemic Sclerosis
TM	Trapeziometacarpal
TNF-β	Tumour Necrotic Factor – Beta
VR	Virtual rehabilitation

Chapter 1: Introduction to the research

1.1. Background

Unimpaired hand function is a critical contributor to the performance of activities of daily living (ADL). Hand function combines aspects of mobility, finger dexterity and strength required to complete tasks. Reduced or lost hand function is related to increased depression, anxiety and stress levels, as well as social isolation (Poole et al., 2013b). It is therefore important to maintain hand function throughout life. Some clinical conditions cause a restriction of finger joint mobility, loss of finger dexterity or strength, thus reducing the ability to perform ADLs.

Systemic Sclerosis (SSc) is a rare autoimmune disease affecting the connective tissues, leading to inflammation, trauma and fibrosis. An autoimmune disease involves the formation of antibodies or lymphocytes against substances which are naturally present in the body. In SSc the immune system becomes overactive, causing an increased collagen fibre production, which then leads to symptomatic thickening and scarring of the affected tissues (Yamamoto, 2009). The symptoms are mostly visible on the skin, in particular at the hands and feet, but it may also spread to the connective tissues of internal organs and blood vessels. Systemic Sclerosis affects approximately 12,000 people in the UK (Scleroderma UK, 2016).

Initially the condition presents as Raynaud's syndrome, where the blood vessels are sensitive to cold, restricting blood flow to the digits. With progression patients experience swelling of the fingers and increased skin thickness and stiffness, resulting in reduced movement ability. As these symptoms are evident at the hands and feet, the patient's ability to use their hands during ADLs is limited (Balint et al., 2014). Hand involvement for patients with SSc is measured in clinics on routine appointments using a range of standardised questionnaires and simple measurements (Lopez Lopez et al., 2014). The score outcome of any measure can then be related to quality of life (if not assessed directly) and inform clinical care. Yet, the scales and questionnaires used do not assess movement throughout the range of motion, but rather the ability to recruit hands during ADLs subjectively or measure finger flexion in general, which reduces their accuracy and inadequately summarises hand function (Lopez Lopez et al., 2014).

Three-dimensional (3D) motion capture to analyse human movement has been used for several decades to inform clinical decision making, especially in cerebral palsy (Simon, 2004). Motion analysis provides a highly accurate and objective mean to assess impairments throughout dynamic tasks, rather than just at a single time point. While discrete values of movement ability, such as range of motion and maximum flexion or extension angles are important, they cannot account for the differences between healthy and pathologic movements throughout a dynamic task. For this purpose, movement indices have been established that allow the determination of deviation from normality of a patient throughout specific movements (Baker et al., 2009; Barton et al., 2012; Schwartz and Rozumalski, 2008). The calculation of movement impairment of the hands in patients with SSc could provide valuable insight to the underlying mechanics that cause an inability to perform ADLs and how these develop after disease onset.

Disease progression in SSc is yet to be completely understood and there is currently no cure. Management options aim to maintain functionality and reduce symptomatic progression of the disease. Most treatment options use pharmaceuticals to target biomarkers or tissues to reduce inflammation, fibrosis or oedema (Distler and Cozzio, 2016). Research further indicates there may be a beneficial effect of hand exercises in addition to pharmaceutical treatment (Willems et al., 2015b; Williams et al., 2018b). Despite this it has been reported that referral to physiotherapy or occupational therapy only occurs in one third of the clinical population, and only 12% actually start and even less adhere to any exercise prescription aiming to improve hand function (Bassel et al., 2012). Further, availability of specialised, targeted exercises is limited (Bassel et al., 2012). Hand stretches, paraffin baths and tissue massages are the commonly suggested interventions (Willems et al., 2015b), but face a low rate of adherence in rheumatology patients (Rannou et al., 2017; Williamson et al., 2017). Virtual rehabilitation (VR) has been used over the past decade to train and improve movement in several conditions, including cerebral palsy, stroke and Parkinson's disease (Barton et al., 2013; dos Santos Mendes et al., 2012; Garcia-Bravo et al., 2019; Garcia-Rudolph et al., 2019; Gumaa and Youssef, 2019). Virtual rehabilitation offers the possibility to create a highly targeted training approach using computer applications. Research in this area has exponentially increased over the past years (Keshner et al., 2019) due to advancements in portable technology, and because it can be used inside or outside of the laboratory. The gamification of rehabilitation exercises showed higher levels of motivation and increased adherence to the intervention across cohorts of multiple ages, clinical populations and genders, in addition to improving motion and motor control of the extremities (Garcia-Bravo et al., 2019; Garcia-Rudolph et al., 2019; Holden, 2005).

1.1. Research purpose

Only few research groups focus on systemic sclerosis despite the severe impact of the disease on the patient's life. Especially hand mobility is a vital contributor to quality of life, and thus any treatment should allow the maintenance or rehabilitation of hand function to ensure a normal or close to normal quality of life. Current rehabilitation programmes are not used due to limited evidence and patients further report boredom and disbelieve of effectiveness of the exercise programmes. Therefore, the overall aim of this thesis was to establish if a new rehabilitation tool, in form of virtual rehabilitation, is suitable for use in patients with SSc, as virtual rehabilitation has shown to increase motivation in other patient cohorts. This design of the virtual rehabilitation tool was determined to be based on objectively measured hand function, rather than the more common, subjective, Likert-scale based assessments, which are frequently conducted in clinical practice but are influenced by outside factors. For this purpose, a 3D motion analysis of hand mobility during functional tasks was conducted. This identified that movement impairments were existent in all joints and all permitted directions of movement. Therefore the computer game for virtual rehabilitation was designed to train all finger joints and permitted directions of movement dynamically at the same time, rather than a stationary stretch of individual fingers as is common in physiotherapy exercises. To make the game portable, and ready to be applied in the patient's home, a portable motion sensor, the Leap Motion controller, was used as a primary input source to drive the game. Finally, the virtual rehabilitation tool was tested in comparison to a conventional physiotherapy approach. While both groups improved in response to exercises, the virtual rehabilitation group showed slightly greater improvements on both objectively measured as well as patient-reported outcome measures. Further the virtual rehabilitation group enjoyed their training programme more compared to the physiotherapy group, suggesting a higher likelihood of adherence to the programme, which would be vital to ensure successful movement rehabilitation.

Chapter 2: Literature review

2.1. Hand and forearm structure and movement

The hand forms the distal end point of the upper extremity and is considered a highly complex anatomical structure. The control of movement is influenced by the musculoskeletal system of the hand and forearm, but also by neural pathways from the brain (Wilhelm et al., 2014).

2.1.1. The musculoskeletal system

The five fingers (thumb, index, middle, ring and little) are structurally referred to by location from lateral to medial in the anatomical position. The thumb is therefore digit 1, the index finger digit 2, the middle finger digit 3, the ring finger digit 4 and the little finger digit 5 (American Society for Surgery of the Hand, 2019). The hand has 27 bones (Figure 1), 134 tendons and ligaments and 17 intrinsic muscles to control fine finger movement (Figure 2a). Hand and wrist movements are further controlled by 18 extrinsic forearm muscles. Nine extensor muscles are located on the posterior aspect of the forearm and eight flexor muscles on the anterior aspect (Figure 2b) (American Society for Surgery of the Hand, 2019; Maw et al., 2016). The 27 bones form 26 joints within the hand, which are split into four categories: intercarpal joints (IC), carpometacarpal joints (CMC), metacarpophalangeal joints (MCP) and interphalangeal joints (IP) (Maw et al., 2016). Of the seven IC joints, three are between the carpal bones of the distal row, three between the carpal bones of the proximal row, while the seventh is located between the proximal and distal carpal bone row (the midcarpal joint). On the proximal end, the scaphoid and lunate articulate with the distal end of the radius to form the radiocarpal joint, which is part of the wrist. The IC joints and CMC joints of digits 2-5 are synovial plane joints and only allow minimal sliding movement between bones (Maw et al., 2016). The thumb CMC joint (Digit 1) is a bi-axial saddle joint between the trapezium and thumb metacarpal. The nature of this joint allows extensive thumb movement in both the sagittal and frontal planes, as well as

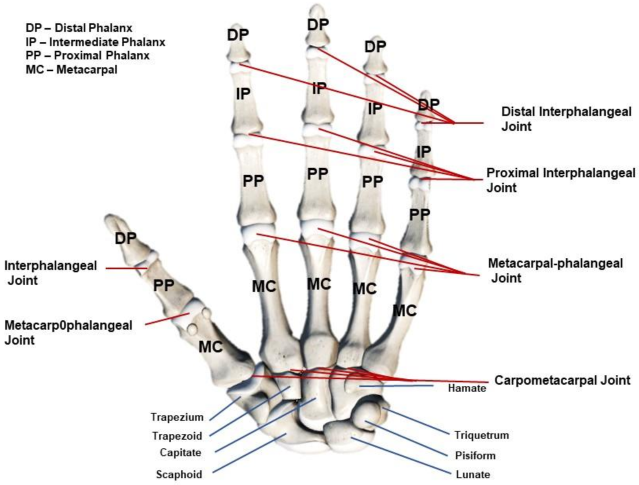

Figure 1: Bone anatomy: the 27 bones of the hand form 26 joints, whereby the intercarpal and carpometacarpal joints of digits 2-5 are immobile plane joints. Movement of the digits is largely due to rotation of the three most distal joints. Image adapted from: Siedlecki (2017).

circumduction. The trapeziometacarpal (TM) joint is therefore structurally and functionally highly distinct from the other CMC joints (American Society for Surgery of the Hand, 2019; Maw et al., 2016). The MCP joints of digits 2-5 are bi-axial condyloid joints supported by palmar and collateral ligaments and allow movement in the sagittal and frontal plane as well as minor circumduction (American Society for Surgery of the Hand, 2019; Maw et al., 2016). The MCP joint of digit 1 is similar to the IP joints. All IP joints and the MCP joint of digit 1 are uni-axial hinge joints and only allow movement in the sagittal plane (American Society for Surgery of the Hand, 2019; Maw et al., 2016). The IP joints of the same finger are controlled by the same muscles and interlinked with ligaments (Figure 3). These anatomical constraints therefore introduce movement limitations, and co-dependency of the IP joints on one another. The distal end of the distal phalanx forms the fingertip of each digit and the end point of the hand and upper extremity (American Society for Surgery of the Hand, 2019).

Anatomically, there are 29 degrees-of-freedom (DoF) leading to several million theoretically possible ways to move our hands. Due to the organisation of muscles, tendons and ligaments the number of movements is anatomically reduced (Hepp-Reymond et al., 1996). Joint capsules and ligaments restrict movement and result in

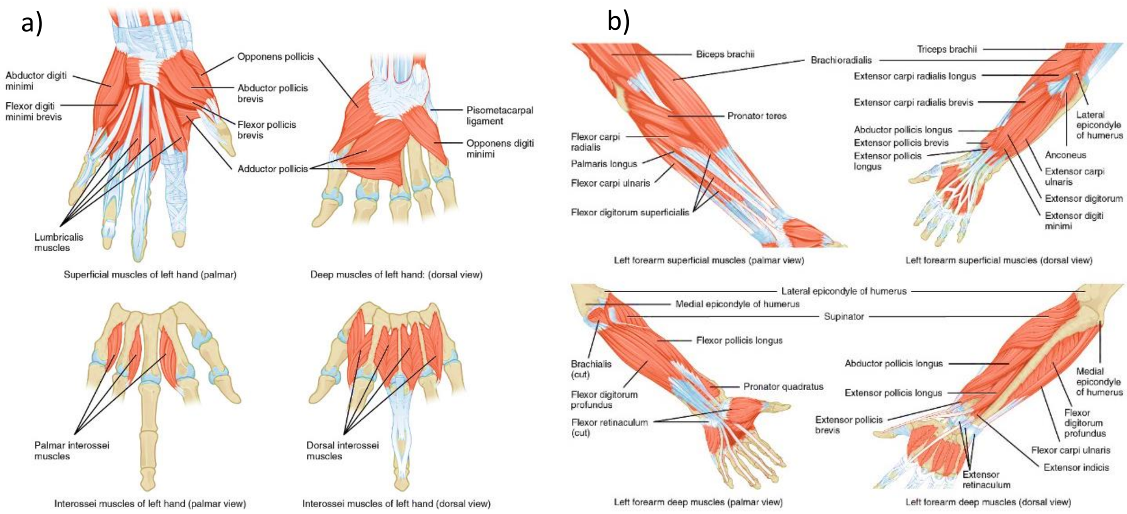

Figure 2: Muscles of the forearm (extrinsic) and in the palm (intrinsic) are activated to initiate rotation of finger bones around their joint axis. Intrinsic muscles are mostly, but not exclusively, involved with the ab-adduction movement, whereby the forearm muscles predominantly control flexion-extension movements as well as all movements of the thumb. Tendons of the extrinsic muscles extend into multiple or single fingers, crossing multiple joints leading to anatomically induced kinematic synergies of the finger joints (Maw et al., 2016). Image from: Betts et al. (2019)

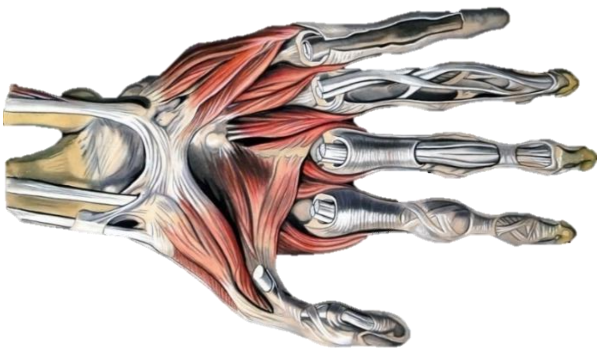

Figure 3: Several ligaments span across the dorsal and palmar aspects of the hand. Ligaments and joint capsules stabilise the long fingers and the metacarpophalangeal joints. The collateral ligaments encapsulate the tendons of the extrinsic muscles, thus contributing to the anatomical constraints of joint movement. Image from: Schorn (1900).

interdependency at the IP joints. The muscles and tendons of the hand further enhance the interdependency as both intrinsic and extrinsic muscles control finger movement. Every joint movement can be controlled by at least two muscles (American Society for Surgery of the Hand, 2019; Maw et al., 2016) and one muscle may control joints of one or multiple fingers. The anatomical constrains induce kinematic synergies, which are further enhanced by neural control patterns (Hepp-Reymond et al., 1996; Wilhelm et al., 2014). Given the anatomy of the hand, joint interdependency and potentially highly individualised motion patters, kinematic models of the hand face several challenges.

2.1.2. Neural control

All muscles of the hand and forearm are innervated by branches of either the radial, ulnar or median nerves extending from the spinal cord (Maw et al., 2016). In the brain, hand movements are initiated in the primary motor cortex (PMC), whereby all neural extensions in the PMC overlap, leading to a strong neural constraint on finger movements (Hepp-Reymond et al., 1996). Lack of selective control over motor unit activation during individual finger movements supports this (van Duinen and Gandevia, 2011) and suggests kinematic and kinetic synergies between fingers (Mirakhorlo et al., 2017; Mirakhorlo et al., 2018; Van Beek et al., 2019; Wilhelm et al., 2014). The dynamic-dominance theory of brain lateralisation, proposes a motor control specialisation to enhance dynamic task performance on the dominant hand and stabilisation on the non-dominant hand (Wilhelm et al., 2014). No gender differences in kinematic measures have been identified for age-matched healthy controls (Coupier et al., 2016), but an age-dependent loss of dexterity (Martin et al., 2015) and increase in kinetic synergies (Mirakhorlo et al., 2018) has been reported. Therefore, when conducting research on kinematic parameters in the hand, age-matched and dominance-matched comparisons are valued over gender-matched comparisons.

2.1.3. Hand dexterity and activities of daily living

Hand dexterity describes the ability to perform and control hand movements, regarding speed, accuracy and stability (Martin et al., 2015). Hand dexterity is therefore important to maintain the ability to perform ADLs. Range and speed of movement, as well as grip strength are the main contributors for hand dexterity, which is known to decline with increasing age (Agnew and Maas, 1982; Van Beek et al., 2019) or in the presence of neural conditions. Due to general age-related muscle loss, grip strength decreases in the elderly (Van Beek et al., 2019). This loss of muscle mass is correlated with a reduced accuracy of movements during reach to grasp and tapping tasks (Hackel et al., 1992). Further, the speed of movement is significantly reduced in the elderly, leading to a large variability in movement duration (Agnew and Maas, 1982; Hackel et al., 1992; Martin et al., 2015). However, the magnitude of dexterity and function loss is gender independent, apart from grip strength where males experience a greater absolute loss in maximal grip capacity. This is likely to be due to a higher maximal grip strength at younger ages, thus the capacity to lose is greater compared to females. On relative terms, Auyeang et al. found that over the course of two years, elderly women

Table 1: Eight common grips, defined by Sollerman and Ejeskar (1995), are used to execute ADLs. The pulp pinch and lateral pinch are the most commonly used grips, whereas the spherical volar grip and extension grip are rather rarely used in daily life. The importance of these grips are equal in the maintenance of independence and quality of life.

Grip type	Description	Example ADL	% contribution
Pulp pinch	Grasping a small object between thumb and index finger	Closing buttons and zippers	20
Lateral pinch	Holding an item between thumb and lateral side of index finger	Holding key to open an item	20
Tripod pinch	Holding an item between three fingers, mostly the thumb, index and middle finger	Holding a pen	10
Five-Finger pinch	Holding an item between the thumb and the other 4 fingers, without palm contact	Lifting a long item	15
Diagonal volar grip	Axis of the object being held is diagonal to the hand	Holding cutlery	15
Transverse volar grip	Axis of item being hold is perpendicular to the hand	Carrying a shopping bag or a hair dryer	14
Spherical volar grip	Grasping and holding a spherical or round item	Opening lids	4
Extension grip	Pinching an item between the thumb and the palm, digits 2-5 are extended	Holding a sheet of paper	2

(64+ years old) lost 10% of their grip strength, while males only showed a reduction by 3.85%. In summary females show a more rapid decrease in grip strength, in addition to a lower absolute strength to begin with (Auyeung et al., 2014).

Holding items, such as pens or cutlery, dressing yourself or picking up small items are tasks that require full range of motion and sufficient grip strength. Analysis of a wide range of tasks has identified eight common grips (Table 1) (Sollerman and Ejeskar, 1995) performed to execute ADLs. A reduced dexterity, due to loss of motor skills, range of motion or strength, will impair the ability to control and perform these grip types.

2.1. Pathophysiology of systemic sclerosis

Systemic sclerosis is a rare, chronic, rheumatic autoimmune disease, affecting approximately 12,000 people in the UK, whereof 100 are children (Scleroderma UK, 2016). Initial symptoms of the disease are swelling of the extremities, Raynaud's phenomenon and coldness. The swelling is thought to be due to an increased permeability of the vascular tissue due to damaged endothelial cells from overly present inflammatory factors. Over time, the skin becomes increasingly sclerotic and either hypo- or hyper-pigmented (Yamamoto, 2009). Abnormal peripheral circulation, affected by the chronic presence of inflammatory factors and autoantibodies, may lead to poor healing and painful digital ulcers, elongated nail folds or pitting (Yamamoto, 2009; Denton and Black, 2004).

Clinically there are three types of SSc: limited SSc (lSSc), limited cutaneous SSc (lcSSc) and diffuse SSc (dSSc). The classification depends on the skin involvement. If the skin involvement is limited to an area above the elbow, the disease is classed as lSSc or lcSSc. If more distal involvement of the skin is evident a patient is classified as dSSc. Whilst there is no pattern in disease progression, lSSc and lcSSc patients show greater involvement of the vasculature and fibrosis, while dSSc is associated with extensive, widespread inflammation and visceral involvement (Yamamoto, 2009; Denton and Khanna, 2017).

While the exact causes for the condition remain unknown, it is hypothesised that the interaction between an aetiological factor and certain gene characteristics triggers an autoimmune cascade. This cascade leads to the release of inflammatory factors, such as cytokines and chemokines. High levels of inflammatory factors lead to activity of the immune system, in particular the fibrocytes, T cells and B cells. If cytokines and chemokines remain active for a long time, this leads to chronic inflammation and the production of autoantibodies, such as anti-nuclear (ANA), anti-topoisomerase Scl-70 (ATA) and anti-centromere (ACA) autoantibodies (Yamamoto, 2009). Autoantibodies are linked to disease classification and level of tissue involvement (Ho and Reveille, 2003). In addition to inflammatory factors, growth factors, especially the self-regulating tumour necrotic factor - beta (TNF-β), is produced in excess (Denton and Black, 2004; Yamamoto, 2009). TNF-β interacts with endothelial cells, lymphocytes, macrophages and fibroblasts and supports the transformation of fibroblasts into myofibroblasts (Yamamoto, 2009; Denton and Black, 2004). Myofibroblasts regulate the production of extracellular matrix (ECM) proteins, including collagen type I and type III. Due to an increase of active myofibroblasts in SSc, ECM proteins are excessively produced, leading to fibrosis of any ECM containing tissue, such as internal organs, muscles and the skin (Denton and Black, 2004; Denton and Khanna, 2017; Yamamoto, 2009). Fibrosis refers to the thickening and scarring of connective tissues. As collagen is a very rigid compound, the stiffness of the ECM containing tissues also increases. Fibrosis in SSc is therefore directly linked to breathing and digestive problems, cardiac conditions and movement impairments. There is currently no cure for the disease (Denton and Black, 2004; Yamamoto, 2009). The American College of Rheumatology

(ACR) and the European League Against Rheumatism (EULAR) created criteria to diagnose the disease based on the presence of disease related factors. These are skin thickening of both hands (score: 9), puffy fingers (score: 2), skin thickening of one finger (score: 4), digital ulcers (score: 2), pitting (score: 2), telangiectasia (score: 2), abnormal nailfold capillaries (score: 2), pulmonary arterial hypertension and/or interstitial lung disease (score: 2), Raynaud's phenomenon (score: 3) and scleroderma related antibodies (ATA, ACA or Scl-70) (score: 3). The scores of the symptoms that the patient exhibit are added up and if the sum of scores is greater than or equal to 9 the patients fulfils the ACR/EULAR criteria for systemic sclerosis (ACR/EULAR, 2013).

2.2.1. Hand involvement in systemic sclerosis

Fibrosis of the skin leads to flexion contractures and other hand deformities. Patients with diffuse SSc (dSSc) experience greater impairments than patients with limited SSc (lSSc) (Erol et al., 2018; Sandqvist et al., 2004b). The most reduced movement is the flexion and extension range, while pronation is close to normal (Bassel et al., 2011; Erol et al., 2018; Sandqvist et al., 2004b). Patients further experience a reduced thumb abduction mobility, which, in conjunction with reduced flexion range, impairs circumduction (Bassel et al., 2011). Finger abduction and volar flexion was also impaired, whereby patients with dSSc experience a greater movement loss than patients with lSSc (Sandqvist et al., 2004b). Further, linking to the reduced flexion and extension ability, the hand span, measured as the distance between the thumb and little fingertips in centimetres during a maximum extension, is significantly reduced in patients with SSc (Erol et al., 2018). The length span is not considered in the Duruoz Hand Index (DHI) used by Erol et al. (2018), but is evaluated in the Hand Anatomy Index (HAI) used by Roberts-Thomson et al. (2006), who found similar values for hand span width. Sandqvist et al. (2004b) recruited the Hand Mobility in Scleroderma (HAMIS) test for the assessment of movement limitations, a test ranking patient ability based on object size they can manipulate. The HAMIS evaluated flexion, extension and thumb abduction movements separately. Bassel et al. (2011) judged the impairment of movement based on questionnaire responses. Truly objective measures comparing patients with SSc to healthy controls are missing in the current literature, yet objectively assessed hand impairment using a goniometer was found to be greater in patients with SSc than in other rheumatic conditions (Lopez Lopez et al., 2014; Poole et al., 2013b). Movement impairments are frequently reported in conjunction with ability to perform ADLs or other clinical parameters associated with SSc.

2.2.2. Patient-reported impact of movement limitations in activities of daily living

Hand deformities interfere with the performance of ADLs which rely on grasp, pinch, and object manipulation. Cinar et al. (2014) evaluated patient ability to perform ADLs using the Evaluation of Daily Activity Questionnaire (EDAQ), whereby a healthy person would report no problems across all tasks (0 points for all tasks), yet there are no concise limits to indicate mild, moderate or strong impairment. The EDAQ evaluates multiple domains and tasks commonly perceived as difficult were related to eating/drinking or the washing category. Opening cans, bottles, glass jars or medicine bottles were among the tasks where patients experienced most limitations. Out of 19 tested participants at least one could not perform these tasks in addition to at least six participants who could only perform the task with much difficulty (Cinar et al., 2014). This finding is supported by multiple other studies (Bassel et al., 2011; Poole et al., 2013b; Sandqvist et al., 2004b; Sandqvist et al., 2014). Opening jars and bottles, as well as carrying bowls, involves the spherical volar grip, which is not commonly addressed in hand function tests. In the category 'Eating/Drinking' patients further commonly report struggles with cutting things and holding a knife and fork of normal size. A coping mechanism is to use utensils with larger grips (Poole et al., 2013b;

Sandqvist et al., 2004b), or to push back the utensils more than usual and use the whole hand to apply pressure (Cinar et al., 2014).

Another very commonly reported limitation is the use of buttons or zips when getting dressed. In the study by Cinar et al. (2014) at least two participants were not able to use buttons or zips. Additionally, at least five participants could only use these items with much difficulty and additional coping mechanisms. A related movement is picking up coins or other small items from a flat surface. Both tasks rely on the pulp pinch. Patients further experienced problems turning a Yale-lock key, relying on the lateral pinch, and writing (tripod pinch). Patients often struggle to write a long text with an ordinary pen and prefer using a thicker pen or an additional sleeve around an ordinary pen to increase comfort. The transverse volar grip offers a base of ambiguity. Patients report they struggle to carry bags or hold a glass yet holding a hair dryer or moving cans is often only mildly impaired (Cinar et al., 2014).

Cinar et al. (2004) interviewed patients regarding their experiences in everyday life following the diagnosis with SSc. Patients described their difficulty to ‘open cans, holding the glasses or other utensils’, which led to one patient even finding herself unable to drink water on her own. The importance of water consumption throughout the day is well known and not being able to perform a crucial task as drinking water bears major risks and limitations. Other patients reported the inability to look after their appearances by brushing their hair or applying make-up (Cinar et al., 2014). This in turn may impact the mental health of patients.

It is evident that all grip types are impaired in patients with SSc, directly impacting their ability to perform ADLs, thus reducing their independence and quality of life.

2.2.3. Assessment of hand function in systemic sclerosis

Clinical assessments of hand function in SSc are conducted during routine clinical appointments. Several functional questionnaires and tests have been validated for SSc or the related disorder rheumatoid arthritis (RA). These vary in length and may therefore not necessarily be useful to apply during a physician appointment, but rather when seeing an occupational therapist or nurse or prior to attending a clinic.

Current measures applied in clinical care are the Finger-to-Palm index (FTP), delta Finger-to-Palm index (dFTP) and the Cochin Hand Function Scale (CHFS). The FTP and dFTP are distance measures of the middle fingertip to the palm during maximum flexion, or the change of distance of the middle fingertip to the palm from maximum extension to maximum flexion respectively, whereby a measure of <0.09 cm is considered healthy, 0.1 - 2cm minimal impairment, 2 - 3.5 cm moderate impairment, 3.5 - 5 cm severe impairment and >5 cm as an end stage of SSc, whereby a change of 0.5 cm is considered clinically relevant (Torok et al., 2010). A healthy magnitude of the delta FTP is difficult to provide as the distance between middle finger tip and palm at full extension is dependent on the span of the hand. If someone can extend the hand into a flat position and flex the fingers to touch the palm this is considered full hand function. Flexion-contractures in SSc are not equally developed in all fingers and joints of one hand. A patient could potentially touch the palm with the middle finger, but not with any other finger, yet still obtain an FTP value of 0, meaning that the patient has the full range of motion. The CHFS is a validated 20-item questionnaire where patients are asked to rank their perceived difficulty to perform ADLs on a scale from 1-5 (Rannou et al., 2007), which also exists as a 6-item short form, CHFS-6. Both tests define a score of 0 as healthy and disease severity increases with increasing scores. For the CHFS the minimal clinically important improvement (MCII) and minimal clinically important difference (MCID) values were determined to be 1.5 and 6.0 respectively (Nguyen et al., 2016). Longer, and more complex hand function tests include the Sollerman Hand

Function Test (SHFT) (Sollerman and Ejeskar, 1995), Jebsen Hand Function Test (JHFT) (Kim et al., 2016), Disorders of the Arm, Shoulder and Hand Test (DASH) (Varju et al., 2008), and Michigan Hand Outcomes Questionnaire (MHQ) (Schouffoer et al., 2016). All these latter tests involve the participant to answer questions and/or rank their ability to perform activities of daily living. Similar, yet not hand specific, is the EDAQ (Cinar et al., 2014; Nordenskiold et al., 1998), used to evaluate the ability of RA and SSc patients to perform tasks of daily living.

These tests vary in length, ranging between six (CHFS-6) and 102 (EDAQ) items, however there is a great overlap in tasks assessed. For example, every test assesses the ability to cut food, whereby the means for this do differ. In the SHFT the subjects actually cut dough, in the JHFT the participants only pretend to cut, and in the EDAQ, MHQ and CHFS the subjects merely rate their ability to cut food based on memory. Five out of six tests also asses the subject's ability to write (tripod pinch), turn a key in a Yale-lock (lateral pinch) and unscrew a lid of a jar (spherical volar grip). The EDAQ even evaluates ability to unscrew lids of containers of various sizes, such as jars, bottles, juice bottles, milk boxes and medicine bottles. Four out of six tests assess the subject's ability to pick up small items (pulp pinch), such as coins or buttons, from a flat surface, and the difficulty experienced when doing up buttons (pulp pinch). Further tasks tested may include grasps relating to the remaining four common grip types – transverse volar grip (for example: holding a telephone, SHFT), diagonal volar grip (for example: turning a screw with a screwdriver, SHFT), five finger pinch (for example: picking up a toothbrush, EDAQ) or the extension grip (for example: turning cards, JHFT).

Even though being different in components, tasks in the aforementioned tests can be split into categories according to which grip is performed (Sollerman and Ejeskar, 1995). The pulp pinch and lateral pinch are the most frequently assessed grips in conventional hand function tests (Sollerman and Ejeskar, 1995). Out of 71 tasks across five functional tests (SHFT, JHFT, CHFS, CHFS-6, DASH), 20 assess the lateral or pulp pinch, 13 times in combination with the lateral pinch. Interestingly, the lateral pinch is never tested in isolated movement, but always in combination with the pulp pinch or the 5-Finger pinch. The 5-Finger pinch is assessed three times individually and three more times in association with the lateral pinch. The tripod pinch is assessed five times on its own (all writing associated tasks) and seven times in combination with the diagonal grip during tasks using knives and forks to prepare a meal. The diagonal grip is further tested four times in isolated condition. The spherical volar grip (seven tasks), transverse volar grip (eight tasks) and extension grip (four tasks) are tested in isolation only. Ten tasks (DASH 6-9, 11, 17-21) were excluded from this evaluation as they referred to tasks that did not target hand mobility and were too vaguely formulated to determine which grip type would apply (Varju et al., 2008).

The EDAQ does not score hand function, but rather ability to perform generic tasks. However, due to the importance of the hands in the ability to perform ADLs over 50% of the tasks tested the EDAQ could also be allocated to specific grips. The other tasks are too vague to be allocated to grips, or are not related to hand mobility. The MHQ evaluated patient perception of hand mobility and pain, and the interference of hand problems with their work and social life, as well as mental health and sleep. Five ADLs are addressed in a short subsection, all of which are also evaluated by any of the aforementioned tests.

In summary, all these tests deliver important information regarding the subjective functional impairment perceived by the patient or the person conducting the test. The current assessment methods lack an objective, quantitative measure to assess overall movement impairments in SSc. The FTP and dFTP are the only objective measures of hand function in SSc, but the insight into overall hand impairment is limited in the presence of finger specific deformities. Flexion contractures may not be equally developed in all the joints of one hand nor are they symmetric between the hands.

Therefore overall hand measures might lack important information of hand mobility and misinform intervention programmes. While subjective measures are important to indicate the patient's perception of disease progression, the use of quantitative measures is vital to the design of rehabilitation programmes. Subjective measures of patients suffering from incurable diseases are likely to be affected by psychological factors. Once diagnosed with an incurable disease, such as SSc, people will undergo several emotional stages, such as outlined by the Kübler-Ross model. A patient's position within the cycle of emotional response will likely influence subjective, questionnaire-based data (Bolden, 2007). Therefore, questionnaires only provide limited insight into the magnitude of impairment and needs to be supported by objective evidence.

2.3. 3D motion analysis

A widely accepted clinical application of motion capture is gait analysis, which is used to enhance the diagnostics from clinical tests, such as body fluid tests, imaging or physical exams (Baker et al., 2016; Davis, 1988; Simon, 2004). The information from motion analysis is used during clinical decision making and to identify suitable treatment options for a patient. Most often, gait analysis is used to assess mobility impairments, and the musculoskeletal contribution to these (Simon, 2004). Motion capture is not only applicable to the lower extremity but has also found applications for clinical analysis of the upper extremity.

Instrumented 3D motion analysis commonly involves the use of passive or active markers, traced by cameras, force plates and EMG electrodes. These systems are expensive and require expertise, in addition to being rather stationary (Simon, 2004). As a cheaper, more portable alternative, 2D video analysis can be used. This approach limits the data to 2D kinematics only (no kinetics), even though movement is three dimensional. Recent developments have combined artificial neural networks and video analysis (Eliason et al., 2019; Kanko et al., 2019) or wearable sensors (Thomsen et al., 2019), to create markerless motion capture devices, which generate 3D motion parameters of the lower extremity. Most approaches are limited to kinematic data, therefore kinetics or inverse dynamics which drive movement cannot be assessed. The benefit of systems using wearable sensors or video cameras is the accessibility to an affordable motion analysis approach outside of the laboratory. This is thought to positively affect the use of motion analysis for clinical monitoring and objectively supported treatment choices (Simon, 2004).

2.3.1. Marker-based motion analysis of the hand

Hand motion capture has been conducted in the past using both marker-based approaches and inertial sensors. Marker-based motion capture of the hand is challenging due to the small size and large number of bone segments to be tracked. Several models have been proposed in the literature to calculate joint kinematics and kinetics from surface-mounted markers (Lee and Jung, 2015). The suggested models were applied in healthy populations to establish finger flexion-extension profiles (Braido and Zhang, 2004), assess age-dependent changes of hand mobility and dexterity, and to mimic functional tasks using grasping of differently sized cylinders (Coupier et al., 2014; Coupier et al., 2016). Hand movement studies with patients are rare. Chiu et al. (2000) applied motion capture to measure the finger range of motion of various finger injuries, ranging from fractures to replantation after total amputation. They demonstrated a poor agreement between motion capture and measurements with a goniometer, whereby the goniometer was the gold-standard (Chiu et al., 2000). Other research groups described movement impairments in Parkinson’s disease (Agostino et al., 2003), and the effect of hand dystonia in this cohort (Curra et al., 2004). In addition to a reduced speed and range of motion, they also demonstrated a deterioration of motor skills with increasing task complexity, suggesting underlying involvement of the PMC, where fine motor skills of the hands are coordinated (Curra et al., 2004). More recently, marker-based motion capture was applied to define the impairments of carpal-tunnel syndrome on thumb movements (Marquardt et al., 2014), showing that thumb opposition and circumduction are impaired while flexion-extension was close to normal. Marker-based motion analysis of the hand has further been used in cadaver studies to validate kinematic models (Biggs and Horch, 1999; Buczek et al., 2011; Carpinella et al., 2006; Cerveri et al., 2007; Kim et al., 2016; Ma'touq et al., 2018), relate muscle activity to movement patterns (Yang et al., 2016), and assess the effect of ligament resection on carpal tunnel syndrome (Eschweiler et al., 2016).

2.3.2. Hand motion analysis using inertial sensors

Over the past decade, pathological hand motion analysis has been conducted using wearable technologies or video-based analysis. Several studies and companies have developed glove-like technologies allowing the assessment of kinematics and kinetics from inertial and force sensor data. Some of these technologies further integrate pressure sensors or electromyography electrodes. The biggest commercial developer for motion capture gloves is CyberGlove Systems LLC (San Jose, CA, USA), who have developed gloves for kinematic and kinetic measurements, as well as tactile feedback. The latest version of the kinematics measuring CyberGlove III™ can further be integrated into virtual reality settings for rehabilitation and measurement purposes. While the company promises high accuracy and precision (sensor resolution <1°, sensor repeatability 3° (CyberGlove Systems LLC, 2010)) , some research based on earlier models demonstrated high error rates in particular at the thumb (Kessler et al., 1995; Quam et al., 1989). This error could be improved by minimising the sensor-crosstalk due to sensor placement optimisation (Kim et al., 2016). Another study shows a median accuracy of 9° (individual joint accuracy ranged from 1° to 23°), and overall precision of 11° of the CyberGlove™, when compared to computed tomography (Buffi et al., 2011; Buffi et al., 2014) . The accepted error of clinical motion data is 5° (Gajdosik and Bohannon, 1987; McGinley et al., 2009), making the CyberGlove™ insufficient for clinical assessments. The cost of purchasing a CyberGlove™ is approximately $30,000. This led to many research groups developing their own instrumented glove-like measuring device to assess hand kinematics and kinetics. Park et al. created a glove with root mean square error (RMSE) ranging between 0.66° and 2.55° across the joints of the thumb, index and middle finger (Park et al., 2017) when compared to a gold-standard marker-based motion capture approach.

2.3.3. Markerless motion capture of the hand

In recent years, video-based three-dimensional motion analysis has become popular. Relying on video input from commercially available sensors, such as the Microsoft Kinect (Microsoft Corporation, Redmond, WA, USA) or the Leap Motion controller (LM) (Leap Motion Inc., San Francisco, CA, USA), computer algorithms reconstruct the underlying skeleton. The LM was designed for touchless interaction with computers and is composed of two video cameras and three infrared LEDs. Based on the video images, an integrated algorithm registers the position of the fingertips and the palm relative to the device, which allows the construction of a full hand skeleton including joint centres. Initial studies determined high accuracy and robustness for the registration of a static pointer, fingertip or palm positions relative to the device in both static (0.2 mm) and dynamic conditions (1.2 mm) (Guna et al., 2014; Weichert et al., 2013). Based on the skeleton and joint centres joint angles can be calculated via the open software developer kit. As the LM is easy to use, without any preparation, some studies investigated the use of the LM as an alternative to goniometers in physiotherapy practices. All studies show poor agreement between the manually and LM measured joint angles. Nizamis et al. (2016) found only significant agreement for the Index MCP flexion range while across all other joints and directions of movement the LM underestimated both flexion (7°-48°) and extension (5°-23°) ranges. They therefore conclude that the LM by itself is insufficient for use in clinical practice to accurately measure joint kinematics (Coton et al., 2016; Nizamis et al., 2018).

Hand motion capture remains a challenge, with the gold-standard still being marker-based motion capture. Portable, markerless approaches using wearable technologies or inertial sensors are deemed to be more readily translatable to applied practice and the accuracy has improved even for low-budget sensors given the technological advancements over the past decades. The trade-off between accuracy and applicability needs to be balanced to meet the study-specific demands. For quick application, portable sensors are more likely to be used, whereas a study requiring high precision and accuracy should be conducted using the opto-electronic motion capture approach.

2.4. Assessment of movement impairment using statistical comparison and indices

To assess the level of impairment in patients, a comparison to healthy controls is common. The principle thereby is similar compared to other medical tests, such as blood sugar tests in Diabetes patients: to evaluate if a patient is hypo- or hyperglycaemic a blood sample is taken and compared to a range that is defined as normal. This normal range had been determined by testing healthy individuals, and as long as the patient's blood sugar level is within the range, no further action is required, whereas, if the blood sugar is too high or low either insulin or glucagon injections or sugar intake is required (DiabetesUK).

When assessing movement impairments in patients the concept remains the same. Normal is defined by healthy, impaired people, who perform the same tasks as later the patients during clinical tests. The movement patterns of the patients may then be compared to the movement patterns of the healthy controls. Unlike a simple blood sugar value, movement is complex as it is time dependent and involves multiple joints and directions of movement are permitted. Therefore a comparison of impaired movement to healthy movement patterns is challenging. Several methods have been comprised over the years, which either use a direct comparison of every assessed parameter or summary indices.

2.4.1. Individual comparison and direct comparison

A direct comparison includes comparing movement curves of patients and a normal data set (typically represented as mean of the healthy data base and the standard deviation) for every parameter of interest. The movement curves may then be visually compared to establish at which point of movement a patient is more impaired and for which specific parameter. For example, when a patient exhibits a stiff knee, the movement curve for the flexion-extension angle is likely to be close to normal during the stance phase but show great differences during the swing phase. This discrepancy is then compensated for in the adjacent joint such as an increase in hip flexion and change in pelvic obliquity. This type of comparison is frequently applied when evaluating gait data in clinical gait reports. A visual comparison can be further enhanced using statistical protocols such as statistical parametric mapping (SPM), which evaluates if the patient movement data is statistically significantly different from the defined normal range for every time point of the movement duration (Donnelly et al., 2017; Pataky, 2010; Pataky et al., 2016). This process can help to determine if even small differences have a significant impairment. Direct visual comparisons, with and without statistical measures, are commonly conducted in gait reports. Gait reports commonly address 9 kinematic movement parameters: pelvic tilt, obliquity and rotation, hip flexion/extension, abduction/adduction and rotation, knee flexion/extension, ankle plantarflexion/dorsiflexion and foot progression (Baker et al., 2016; Barton et al., 2012; Schutte et al., 2000; Schwartz and Rozumalski, 2008). These parameters have been identified as most critical contributors to lower extremity impairment. For the upper extremity and hand this level of information is missing and a direct comparison of the hand would at the moment include all joints and permitted ranges of motion, resulting in 20 angles, velocities and accelerations (60 curves in total) per hand. This level of detail might be incomprehensible and requires a long time to interpret, making this type on comparison unsuitable for translation in clinical practice for hand function.

Direct comparison can further be assessed using statistical tests on discrete values, such as range of motion, peak or minimum values. The use of discrete values is a widely discussed issue in biomechanics as movement does happen dynamically over time and the evaluation of a single value might dismiss other important temporospatial characteristics. At level of the hand, it is further important to acknowledge the existence of a hierarchical kinetic and kinematic chain, where no finger movement is truly independent. As any joint movement affects and is affected by other joints, the use of direct comparisons and discrete values might not be necessary.

2.4.2. Movement impairment indices

Indices aim to summarize the level of impairment into a single value, as a single value is comprehensible and easy to understand, thereby allowing the translation of science into clinical practice. Multiple indices have been developed using various mathematical and biomechanical approaches.

In the lower extremity the importance of specific discrete values is well known, such as the peak knee abduction moment which is link to knee pain and osteoarthritis. This knowledge was used by Schutte et al. (2008), who created the Gillette Gait Index (GGI) which aimed to summarise movement impairment of the lower extremity based on 16 discrete values measured during a single gait cycle. The GGI is based on knowledge of established research which addresses how movement impairments in one joint link to impairment and compensatory mechanisms in other joints. This type of information is currently lacking for the upper extremity and hand. Thus the translation of the GGI to the upper extremity will require more research on the impact of the kinetic and kinematic chains affecting its movement. While the GGI is based on discrete values, which represent a limitation on their own, other movement indices include information of the whole movement phase.

The Gillette Gait Index (GDI) (Schwartz and Rozumalski, 2008) scores the level of impairment out of 100, whereby 100 means there is no impairment. The score is determined by calculating the Euclidean distance between patient data a healthy control mean vectors, which are the result of a singular value decomposition of key kinematic variables of gait. Thus, the greater the distance between the vectors, the greater the impairment of the patient is. The GDI considers the whole movement curve, however, the mathematical concepts underlying it are complex. Further, similarly to the GGI, the GDI relies on established knowledge of the gait impairments in the lower extremity.

While the GDI shows good correlations to the GGI, the complexity limits its translation to clinical practice as the meaning of, for example, 2.5 standard deviations from normal as well as the underlying mathematical principles can be difficult to understand by clinicians. This was addressed by Baker et al. (2009), who developed the Gait Profile Score (GPS). For this index the root mean square error, a measurement of distance between curves, was used. The distance has the same unit as the original curves, therefore the GPS can provide a summary distance value for every curve in, for example degree. These units are easy to comprehend, making this tool easier to understand for clinicians compared to the GDI. The GPS can be calculated for every single curve, followed by the calculation of a mean value to determine the overall level of impairment in a single GPS mean value. However, this summary can be challenging if different types of data are used, as for example velocities and angles have very different magnitudes. Therefore a change in velocity would have a greater impact than a change in angular magnitude.

The GGI, GDI and GPS (Baker et al., 2009; Schutte et al., 2000; Schwartz and Rozumalski, 2008) have two limitations in common. The first one is that they compare patient data relative to the healthy control mean. Considering the example of blood glucose levels again, abnormal glucose levels are defines as falling outside a range not by distance to the middle value of the healthy range. For example, the normal blood glucose range is 4.0 to 5.9 mmol/L, with the normal middle value being 4.95 mmol/L (DiabetesUK, 2020). If a Diabetic patient has a value of 6.0 mmol/L the blood level is close to normal despite being over 1 mmol/L away from the mid value of the healthy range. Therefore, when comparing to a middle or mean value, the variation of a healthy control population is not taken into consideration, which would overestimate the actual level of impairment. The second one is that they sum up curves into a single value, thereby making it difficult to understand at which phase of the movement a patient is more impaired.

The movement deviation profile (Barton et al., 2012) recognised these and addressed these issues. The movement deviation profile allows the calculation of distance between a patients' movement curve and the closest matching healthy control data point. By comparing to the closest matching control data point the patient data is effectively compared to the end point of the range of normality rather than the mean, reducing the likelihood of overestimating movement impairments. The deviation from normality can further be calculated for every time point of a temporospatial movement curve, thus showing at which time point patients deviate from normality. The deviation from normality can further be summarised in a single value, to ease understanding by a clinician.

In summary, there are several means to assess the level of impairment in clinical cohorts. Currently existing indices have been exclusively developed for the lower extremity, yet the importance of the upper extremity in everyday life should give enough reason to develop upper extremity indices as well. Direct comparisons might be incomprehensible, but also not be required given the hierarchical chains. Therefore indices, evaluating multiple joints at once, may offer a good solution. While all presented indices are theoretically mathematically translatable to the upper extremity there are certain factors that make them unsuitable for the hand. The GGI is based on specific discrete values, which have not been established for the hand. The GDI and GPS compare patients to a mean value rather than a range of normality, in addition to providing no insight into the timing of impairment during dynamic tasks. There is no evidence if patients with SSc struggle more during specific movement phases, and this needs to be evaluated. This suggests that the MDP might be the most useful tool to assess hand movement impairments objectively with an index.

2.5. Hand mobility rehabilitation in rheumatic disorders

Hand therapy is the non-surgical management of hand conditions, including the training of hand and finger mobility and strength. The hands are commonly impaired in rheumatoid conditions, including RA and SSc. The conventional approach to hand therapy involves a combination of physiotherapy and occupational therapy (The British Society for Surgery of the Hand, 2019). While physiotherapy engages in stretching and strengthening exercises for joint mobilisations, occupational therapy focusses on ADL execution and regaining lost function (The British Society for Surgery of the Hand, 2019). Information for hand exercises is abundantly available, with condition-specific charities and healthcare organisations suggesting disease specific exercises (NHS Inform, 2019; Scleroderma and Raynauds UK, 2016; Scleroderma Foundation, 2019). Yet, rheumatology healthcare professionals are hesitant to provide advice on exercise in rheumatic conditions. This has led to an urge of education for specialist clinicians and nurses to provide trivial information to patients (Hurkmans et al., 2011; van Eijk-Hustings et al., 2012).

2.5.1. Effectiveness of hand stretches in rheumatic conditions

The effectiveness of hand exercises and hand therapy in chronic conditions has been tested widely in the literature. The Stretching And Strengthening for Rheumatoid Arthritis of the Hand (SARAH) exercise programme (Williams et al., 2015; Williamson et al., 2017) indicated benefits of hand exercises for patients with RA after 12 months (Williams et al., 2015) on finger mobility, self-efficacy and work ability. Measured with the MHQ, overall hand function showed an initial improvement after four months of 7.28 points for the exercise group and 4.34 for the usual care group, which is less than the minimal clinically important difference (London et al., 2014; Shauver and Chung, 2009), whereby the exercise groups almost reaches the MCID threshold of 8. At 12 months follow-up, these changes compared to baseline measures with 7.59 points for the exercise group, and 4.22 for the usual care group, reflecting no further improvement on the MHQ scale. This finding was consistent across all sub-categories of the MHQ, including ability to perform ADLs, self-efficacy and pain. Compared to patients receiving the usual care, patients receiving the exercises showed greater improvements in grip strengths at four months (Exercise: 15.55 N; Usual care: 7.35 N). Similar to the MHQ scores, these changes were maintained, but not further improved at 12 months follow-up (Exercise: 15.77 N; Usual care: 9.57 N) (Williams et al., 2015). Therefore both groups show changes in grip strength which are below the suggested, general MCID of 5 - 6.5 kg (Bohannon, 2019) or 49.03 N – 63.74 N. Finger dexterity, as assessed with the nine-hole peg test, did not chance significantly within the groups at four months follow-up (Exercise: -1.39 s; Usual care: -0.79 s, whereby a negative score reflects improvement, $p = 0.07$). The normal score is 18 seconds to complete the test, and the minimal clinically significant change is high (32.5 seconds), suggesting that neither chance is clinically significant in addition to being statistically insignificant (Chen et al., 2009). Again, this was not further enhanced at 12 months follow-up. Range of motion, measured with a goniometer, showed similar patterns with initial improvements at four months follow-up, which were maintained but not further improved at 12 months follow-up (Williams et al., 2015). Upon extended follow-up between 19-40 months, they could not report a further improvement, but rather a decline in hand function. They associated this with a reduced adherence after the initial 12-month test period (Williamson et al., 2017). Short-term improvement in hand function after exercises is supported by multiple other studies (Williamson et al., 2015). In addition to several original studies, three extensive systematic reviews have evaluated the effectiveness of exercises in RA, and concluded that grip strength is most likely to improve after exercises, as well as dexterity and to a lesser extent range of motion (Bergstra et al., 2014; Hammond and Prior, 2016; Wessel, 2004; Williams et al., 2018b), whereby no study exceeded the minimal detectable change for finger range of motion, which was found to be between 12° - 30° when measured with a goniometer, varying for different joints (Reissner et al., 2019). As MCID are not met the evidence for the beneficial results is classed as very low to moderate quality, in addition to low statistical power and limited sample sizes or because it is not conducted to the highest qualitative standards (Hickey et al., 2015; Williams et al., 2018b). Most studies rely on subjective measures. Therefore the integration of objective measures would improve the quality of research. None of the aforementioned original studies or reviews report adverse events, suggesting that exercise should be researched further as there is most likely no harm.

Despite being closely related to RA, only very few studies have evaluated the effectiveness of exercises in SSc. While the first studies suggesting positive effects on range of motion, stiffness and grip strength date back several decades (Rudolph et al., 1974), there is only limited evidence for the effectiveness of SSc specific hand exercises in the current scientific literature. In particular there is a lack of large cohort, long-term follow-up studies regarding the effectiveness of exercises in SSc, with only one multi-centre RCT available. This study indicates short-term beneficial effects of hand exercises at one month, but no prolonged effect at 12-month follow-up (Rannou et al., 2017). Similarly, a case study by Carr et al. showed no change in hand function after 12 months consistent exercises (Carr et al., 1997). Short-term improvements in hand function (Antonioli et al., 2009; Horvath et al., 2017; Piga et al., 2014; Poole et al., 2013a; Schouffoer et al., 2016), ability to perform ADLs (Horvath et al., 2017; Poole et al., 2013a; Schouffoer et al., 2016), ROM (Horvath et al., 2017; Mugii et al., 2006; Mugii et al., 2019) and grip strength (Antonioli et al., 2009; Horvath et al., 2017; Schouffoer et al., 2016) were identified in multiple other case studies and small cohort studies (between 8-53 participants). Follow-up period for these studies were between one to six months. Only Mugii et al. (2019) included a one-year follow-up measurement of the passive range of motion and could detect further improvements or maintenance of the passive ROM. It is not possible to state if the measured ROM thereby exceeds the MCDI of goniometer-based ROM measures as the sum of the range of motion of the MCP, DIP and PIP joints is given rather than the individual joint-specific ranges.

2.5.2. Effectiveness of wax baths and manual therapy

Paraffin wax baths are a common non-pharmacologic intervention for SSc, but the literature presents conflicting evidence. An initial study demonstrated instant, positive changes in hand function after the application of paraffin wax baths (Askew et al., 1983). The beneficial effects of paraffin baths on grip strength, range of motion and pinch strength have since been reported in many studies, evaluating the efficacy over one to three months (Mancuso and Poole, 2009; Pils et al., 1991; Sandqvist et al., 2004a), in one case in combination with exercises (Sandqvist et al., 2004a). Yet, when delivered in conjunction with hand exercises, paraffin baths have no additive, beneficial effect (Gregory et al., 2019) contrasting findings from Sandqvist et al. (2004a). The differences in outcome might be explained by the respective study designs. Both studies used the same tools (HAMIS, SHAQ and modified Rodnan Skin Score (mRSS)) to assess the effectiveness of the intervention. The MCDI for the HAMIS is unknown however established for the mRSS (3.2 to 5.3) (Khanna et al., 2019; Khanna et al., 2006) and SHAQ VAS (0.10-0.14) (Pope, 2011) in the literature. Gregory et al. (2019) (SHAQ VAS overall: 0.17 and 0.14, mRSS: no change; (experimental and control group change respectively)) and Sandqvist et al. (2004a) (SHAQ VAS overall: 0.26 and 0.14, mRSS: no change reported; (experimental and control group change respectively)), thus both found clinically significant improvements on the SHAQ scale but not the mRSS. Sandqvist et al. (2004a) applied the intervention to one hand, using the contralateral side as a control, whereas Gregory et al. (2019) used two different groups. It is possible that patient responses to treatment are individual, potentially making the use of the contralateral hand as a control more suitable for assessing the effectiveness of exercises. Further, the exercise programme used by Sandqvist et al. (2004a) included more exercises, as well as targeting individual fingers whereas Gregory et al. (2019) relied on only three exercises targeting all fingers simultaneously. The participants by Sandqvist et al. (2004a) completed the exercises once daily, after the wax bath, on both hands, whereas Gregory et al. (2019) instructed their participants to complete the exercises 3-10 times a day. The wax bath procedure was the same in both studies, but Sandqvist et al. (2004a) used daily wax baths, whereas Gregory et al. (2019) instructed their participants to use the wax time at least four times a week. The wax bath frequency could potentially influence the skin and enable greater benefits of following exercises.

Manual therapy in the form of tissue massages (Maddali Bongi et al., 2009) or lymph drainage (Bongi et al., 2011) have also shown short-term beneficial results at one month or five weeks respectively. While the improvement in passive ROM after tissue massages was maintained for 12 months, the overall functional scores assessed with the Scleroderma Health Assessment Questionnaire (SHAQ) were not improved.

2.5.3. Rehabilitation programmes: referral, adherence, and intensity

The lack of high-quality evidence of especially long-term beneficial results of hand exercise on functionality might explain the reported low referral rates for patients with SSc (Bassel et al., 2012). The cost of supervised rehabilitation is high and thus referrals are less likely to happen if no rigid evidence supports the need or benefit of exercises. Multiple recent studies have evaluated the use of mail-delivered or self-managed exercise programmes in rheumatoid patients (Brorsson et al., 2009; Hoenig et al., 1993; Lamb et al., 2015; Manning et al., 2014; Mugii et al., 2006; Mugii et al., 2019; O'Brien et al., 2006; Piga et al., 2014; Poole et al., 2013a; Schouffoer et al., 2016; Williams et al., 2015). The benefit of these exercises is that they can be often performed at home without expensive equipment or supervision, thereby increasing the availability of exercises to immobile patients. While the programmes are economic and cost-effective (Hammond and Prior, 2016; Manning et al., 2015; Williams et al., 2015), the self-directed completion of exercise results in lower adherence rates compared to supervised exercises by a healthcare professional. A semi-supervised or remotely monitored programme could potentially provide a base for improved adherence, and ensure that the patients have regular contact with a clinician. In the SARAH trial, 71% of all patients in the exercise group reported to perform exercises at least three times per week for the first four months, and only 12% reported they did no exercises. After 12 months, only 39% completed exercises four times per week, and after an extended follow-up period only 31% were still completing the exercises. Simultaneously, at 12 month 27% reported not to do any exercises, which increased to 38% during the extended follow-up (Williamson et al., 2017). The changes in amount of exercise were matched with corresponding reductions in hand function as measures with the MHQ.

Similar rates of drop out and low adherence were identified for patients with SSc (Rannou et al., 2017), while participants in other self-administered studies reported good adherence to their programme (Poole et al., 2013c). As long-term beneficial effects can only be established by consistent performance of exercises, adherence to the rehabilitation programme is trivial. One research group has established a tele-monitored exercise programme, combining supervised and non-supervised exercises with online monitoring. However, while they list supporting evidence in the protocol design, this programme has not been tested yet in patients with SSc (Wolff et al., 2014). The combined structure could potentially improve adherence.

At the moment exercise guidelines for hand rehabilitation are drawn from expert opinion, rather than a scientific rationale. Current hand specific studies offer either no guidelines for time (Landim et al., 2019), or state up to 50 minutes on five days per week (Piga et al., 2014). In context of aerobic capacity and strength training in SSc the recommendations range twice a week for 30 minutes high-intensity interval training (Mitropoulos et al., 2018) to three times a week 80 minutes (combines aerobic and strength exercises) (Alexanderson et al., 2014), whereby most studies refer to three days per week in patients with SSc (Liem et al., 2019). Studies in rheumatoid arthritis have shown that high-intensity exercises (3+ times per week) show better results than programmes involving only exercising once a week, yet, too high time demands are a reported barrier to adherence. Overcoming the time-commitment barrier for exercises is reported not only for SSc but also many other conditions, as well as healthy people when attempting to become less sedentary. By identifying more engaging and enjoyable activities people report greater motivation to complete the exercises regularly, as the perceived time burden is lower. This concept is applied to virtual rehabilitation, where the rehabilitation exercises are translated into a playful game environment. Therefore, completing virtually based rehabilitation could be a solution to overcome the time demand motivational barriers that high-intensity rehabilitation programmes with three or more sessions a week currently face.

2.6. Gamification of rehabilitation

The gaming industry is an ever-growing industry expecting to exceed 90 billion net worth in 2020. There are over 2.5 billion regular gaming participants world-wide (WePC, 2019). Mostly these games are used for entertainment, but since the 1980s video games have also been integrated into the treatment or rehabilitation plan of patients. One of the earliest studies in this field compared the effects of playing video games and playing with regular toys during chemotherapy on nausea levels in paediatric cancer patients. The video game group showed less nausea during a chemotherapy session compared to the control group playing with regular toys (Redd et al., 1987). Clinical treatments, such as chemotherapy, are painful, and can have several negative side effects, such as nausea. The ability of video games to distract the mind and relax the patient to the extent that they perceive less suffering was used to justify further research into virtual concepts during treatment and rehabilitation (Kato, 2010).

While initially being played as a distraction, over the past decades the integration of movement into the games has changed the concept of gamification of rehabilitation. Levering technological advancements, commercially available movement sensors allow the integration of motion patterns into games, making virtual rehabilitation (VR) useable for physical rehabilitation of motion patterns or movement control. Beneficial effects of virtual rehabilitation of movement control and range have been identified for the full body in various conditions, such as postural control, balance (Brien and Sveistrup, 2011), gait characteristics (Cho et al., 2016) and arm function (Chen et al., 2014) in children with CP. Other studies have shown faster rates of rehabilitation after total knee arthroplasty, as the HSS knee scores and knee range of motion improved faster over time in the VR group compared to conventional physical therapies (Jin et al., 2018). One of the first applications of VR in a context of physical therapy was during the rehabilitation of arm injuries (Kato, 2010). The upper extremity, including hand function, is frequently addressed in VR context, in particular for patients recovering from stroke (Cameirao et al., 2016; Laver et al., 2015). In patients with stroke, virtual rehabilitation training on a Microsoft Kinect showed significantly greater improvement in dexterity as assessed with the Fugl-Meyer Assessment and active ROM as measured with a goniometer, compared to physical therapy (Askin et al., 2018). Other studies found improvements in hand strength and function following six weeks of virtual reality-based training (Lee et al., 2016). These outcomes were objectively assessed using the Box-and-Block test for dexterity and strength, as well as the JHFT and grooved Pegboard test. Compared to conventional therapy, there was no significant difference for effectiveness. This is supported by other randomised controlled trials (Brunner et al., 2017; Ikbali Afsar et al., 2018), who found improvements in upper extremity function of VR groups to be of similar to that of conventional therapy groups, whereby a combined approach of VR and therapy has been shown to be the most effective to rehabilitate arm movements in stroke patients (Corbetta et al., 2015; Kiper et al., 2018). Interestingly, in sum, as described by multiple meta-analysis and systematic reviews, virtual rehabilitation does show greater improvements compared to conventional therapy for Parkinson’s disease (Triegaardt et al., 2020), stroke (Corbetta et al., 2015), spinal cord injury (Abou et al., 2020), multiple sclerosis and cerebral palsy (Cano Porras et al., 2018) for various outcome measures (balance, dexterity, range, strength) related to movement and motor control.

Recently the use of VR goggles for a fully immersive experiences have been used, while in earlier days a simulated 3D environment presented on a 2D screen was used. Yet, despite the various tools and forms or presentation, the concepts of virtual rehabilitation (VR) can be applied to a wide field of conditions. Mostly these are linked to motor rehabilitation, whereby a neurologic deficit is retrained during therapy, such as in stroke, cerebral palsy or Parkinson's disease. Systemic sclerosis (SSc) is not classified as a neurologic condition, yet several studies have suggested a neurologic involvement for the upper extremity due to a reduced use of the arm and hand following the onset of symptoms (Amaral et al., 2013).

As motor learning is forming a common denominator across virtual rehabilitation studies for various purposes and conditions, the foundation and scientific rationale for virtual rehabilitation studies is based on the same concepts and key domains relevant to motor learning: motivation, feedback and repetition (Holden, 2005). These domains are considered vital for the success of virtual rehabilitation concepts.

2.6.1. Adherence to rehabilitation and motivation

It has been reported that many patients, regardless of age, gender or condition do not comply with a prescribed treatment plan. This treatment plan may be linked to medication or more physical interventions such as rehabilitation exercise programmes. The lack of adherence may be linked to physical signs, such as nausea, pain, or other strong side effects or time and planning demand and lack of support. Further the psychological aspect, linking to motivation, perceived benefit and enjoyment cannot be underestimated (Kato, 2010). People tend to give priority to tasks that they enjoy or are motivated to complete. Video games provide enjoyment, entertainment and challenges which can potentially be a therapeutic benefit, and also increase adherence to a treatment or rehabilitation programme. Given that the changes by the respective programmes are similar in magnitude or even greater than in conventional therapy (Brunner et al., 2017; Cano Porras et al., 2018; Corbetta et al., 2015; Ikbali Afsar et al., 2018; Kiper et al., 2018; Triegaardt et al., 2020), the benefit of increased motivation, thus likelihood of adherence, provides a further favourable edge to the concept of game-based rehabilitation.

Motivation is a complex term, and evolves around the reasoning behind human action. There are various mechanisms through which human behaviour may be adapted through internal, self-regulated or external sources (Souders, 2019). Internal mechanisms, such as enjoyment, wanting to achieve a goal, and thrive for perfection/excellence are relying on the person's perception as well as resilience. In health rehabilitation these could be associated with wanting to improve their health status, movement ability or independency. External factors, such as supervision by an instructor, or external sources providing emotional 'kicks' on the other hand are not self-controlled and may trigger various responses, typically towards an increase in willingness to work towards a goal (Souders, 2019). Motivation is vital for adherence to exercises, regardless if for sporting excellence, health reasons or rehabilitation purposes, or any other non-physical activity in order to achieve a goal. Motivation can thereby be seen as a willingness to endure potentially painful practice to see a result (Holden, 2005). While pain, discomfort or other negative side-effects may be off-putting, a high motivational level can overcome these negative emotions to achieve a long-term result. It is assumed that motivation and engagement in game-based interventions is greater compared to conventional therapy. This is associated with the playful environment and instant feedback on ability, when compared to repetitive exercises without feedback (Kato, 2010).

2.6.2. Feedback and repetition of virtual rehabilitation instruments

Feedback and repetition are integral parts to learning and apply to all skill developments throughout life (Bruner, 2001). For example, elite athletes practice multiple hours a day to achieve their goals or learning a new language requires multiple months or years. Skill acquisition, whether it is a physical or mental challenge, requires time, which is linked to repetitions. For example, when learning a language, one typically has to repeat vocabulary more than once in order to remember it in the future, and a swimmer needs to swim a stroke more than once in order to improve. The number of repetitions thus increases the likelihood of acquiring a skill (Bruner, 2001). While the amount of practice, thus number of repetitions, is important to improve, feedback is essential to ensure that what is practiced actually aids the progression to the next level. For example, one could learn a vocabulary but actually pronounce it wrong or use it wrong in sentences and a swimmer might be swimming the stroke with an inefficient movement pattern. In those cases, all repetition is worthless as the learned skill is still incorrect. Feedback, whether it is verbal from an external source or intrinsic through our senses, allows the correction of a learned skill to bring one's skill ability to the next level and is therefore central to learning (Sunaryadi, 2016). Yet, too much feedback can be detrimental as well, and children are likely to require more feedback for skill acquisition compared to adults (Sullivan et al., 2008). Therefore the amount and presentation of feedback needs to be tailored to different purposes.

In rehabilitation exercises the same concepts apply: a goal towards improved control or range of motion can only be achieved by frequent repetition of correct movements, which are driven by feedback mechanisms. For virtual rehabilitation concepts the feedback is typically linked to the senses, such as visual, audio, haptic, mechanoreceptive (vibrations) or proprioceptive feedback. Feedback can show a patient, in real-time, if their movement is correct or successful, depending on individual game design. The real-time bio-feedback thus provides an indication of ability, for example an increase in points gained shows a greater ability, or a sound might be associated with an error that happened in the game and thus the patient knows they made a mistake and will try to avoid this in the future. On a neurological level the adaptations to bio-feedback lay in the primary motor cortex, where any movement is controlled (Holden, 2005). In response to neuroplastic changes, an alteration in firing pattern from the PMC to the muscles that are trained by a game leads to a tighter control of the movement executed, whereby a tighter control relates to more precise movement patterns and is linked to successful rehabilitation of movement control (Darekar et al., 2015; Holden, 2005).

Real-time bio-feedback provides direct feedback to the patient, compared to potentially long times of waiting to see visible changes in conventional physiotherapy. This type of feedback thus can increase the motivation to continue the exercises, which in turn will lead to further improvements and more motivation. Therefore repetition, feedback and motivation are interlinked, yet separate pillars, for any form of learning, including motor learning in rehabilitation settings.

2.6.3. Application of virtual rehabilitation in rheumatic conditions

Despite the ability to improve hand function using VR concepts, there is currently no data in the literature assessing the effectiveness of VR in rheumatoid conditions which lead to hand mobility impairments, such as SSc, or the more common rheumatoid arthritis. Yet, given the neurologic involvement (Amaral et al., 2013), virtual rehabilitation should be considered as a potential rehabilitation approach.

All the described benefits of VR are only achievable if the intervention programme is targeting the correct therapeutic outcome measure. Therefore, commercially available games might not be useful unless tailored to a specific task or the integration of other components. As every rehabilitation programme, VR requires tailoring to individual patients or disease categories (Burdea, 2003; Kato, 2010; Merians et al., 2014; Rogers et al., 2019). If applied correctly, VR can be used to train control of movements in a particular range and indirectly also functional ability (Rogers et al., 2019), whereby the evidence for the latter is limited (Merians et al., 2014).

In summary, virtual rehabilitation has been shown to raise levels of adherence to treatment plans across a broad range of patient cohorts, by increasing levels of motivation and providing feedback, which the patient may experience through their senses. Further, VR had greater or similar effects on the range of motion and control of movement when compared to conventional therapies, partly by providing a relatively high number of repetitions. These effects are only possible if the game applied in the VR context targets the correct therapeutic outcome measures.

2.7. Summary

The highly complex hand is significantly impaired in patients with SSc, leading to increased dependency, anxiety, depression, and a reduced quality of life. The assessments used in clinical practice are subjective to the patients' perception of their disease, or do not measure all fingers. The assumption of equally developed flexion contractures of all joints within a hand makes the only truly numeric measure of hand function, the finger to palm index, inadequate. Three-dimensional motion capture is a validated tool for clinical assessment, but has not yet been used for hand mobility assessments in SSc. Given the importance of the hands in everyday life, a research focus has been established to maintain or improve hand mobility in patients with SSc. The adherence to the exercises is low, as patients name the common barriers to commit to an exercise programme: time demand, feeling no improvement, difficulty to prioritise boring exercises. Gamification of exercises using virtual rehabilitation has been associated with increased levels of motivation and adherence. A customised game for hand mobility training in SSc could therefore potentially overcome some of the named barriers of adherence.

2.8. Aims and Objectives of the research

The overall aim of this research thesis was to assess the suitability of virtual rehabilitation as an intervention method to reduce hand movement impairments in patients with SSc. To address this aim, several smaller aims and their objectives were implemented over the course of the research programme:

1. Assess the hand movement limitations of patients with SSc during functional tasks using three-dimensional motion analysis.
    a. Movements of the patients will be compared to healthy controls to measure the difference in joint kinematics during dynamic, functional tasks. The difference will be assessed using a movement impairment index to measure the impairment of the whole hand as well as specific joints and movement directions. It is hypothesised that patients will show significantly different movement patterns compared to healthy controls and that some joints will show a greater impairment than others. The impairment, as measured with the index, will be correlated to current clinical measures of disease progression to devise a simple, translatable measure of mobility impairment for clinical practice. It is hypothesised that at least one measurement correlates strongly and significantly to the objectively quantified level of movement impairment.
2. Develop a portable method to capture 3D movement of the hand
    a. Identify a cheap sensor or input source to assess hand kinematics, particularly angles during dynamic tasks in real-time, which is small and easy to deploy outside of the laboratory. This will be achieved by exploring commercially available sensors, where the data stream can be accessed by third-party software for further use in external programmes. Once in a third-party software, the data can be

manipulated to meet the demands of a study or compare to other motion capture tools, such as an opto-reflective marker-based motion capture approach.

3. Deploy the portable method into a virtual rehabilitation context
    a. The design of the virtual rehabilitation tool should be informed by the outcome of the motion assessment from Aim 1. Following the design of the game itself it needs to be adjusted to be driven by the input data from the portable motion capture tool. The virtual rehabilitation tool should therefore train previously identified movement limitations using real-time data from the portable motion capture system.
4. Examine the effect of the virtual rehabilitation tool in comparison to traditional physiotherapy on hand movement limitations.
    a. In a randomised controlled trial with two groups of patients the previously designed virtual rehabilitation tool is to be compared to already established physiotherapy exercises to determine if there is a therapeutically, beneficial effect of the novel intervention compared to traditional one. The effectiveness of both exercise interventions is assessed using objective motor control and motion analysis as well as subjective, patient-reported outcome measures. It is hypothesised that both groups will show an improvement in hand function across all tests, whereby the virtual rehabilitation group shows a significantly greater improvement across all measures as well as likelihood of adherence to the exercises.

2.9. Thesis structure

This thesis combines experimental and technical chapters. The diagram below (Figure 4) illustrates the structure of the thesis chapters as well as the addressed aims of the individual chapters and specifically which chapters link together. The developmental chapters are highlighted in green to set them apart from other literature based and experimental chapters.

Thesis structure

Chapter	Title	Structural design	Addressed Aims	Linking to Chapters….
1	Introduction to the research			
2	Literature review	Literature review		3, 4, 5, 6 ,7
3	Describing the development of an opto-electronic and a markerless motion capture approach for the hand and subsequent kinematic modelling	Developmental study: Technical chapter outlining the design of kinematic models used in this thesis		4, 6 and 7
4	A comparison of hand movements during functional tasks in patients with systemic sclerosis and age- and hand dominance-matched healthy controls	Experimental study: Comparing hand movements of patients with SSc to age-matched healthy controls to quantify joint specific movement impairments	**Aim I:** Accurately assess the hand movement limitations of patients with SSc during functional tasks using three-dimensional motion analysis	5 and 7
5	Method chapter: Design of a virtual rehabilitation game for systemic sclerosis informed by three-dimensional movement analysis	Developmental study: Technical chapter with a detailed description of the design of a virtual rehabilitation tool for patients with SSc	**Aim III:** Deploy the portable motion capture method into a virtual rehabilitation context	7
6	Improving the accuracy of the Leap Motion controller for purposes of markerless hand motion capture using artificial neural networks	Experimental study: Assessment of the Leap Motion controller to accurately measure hand kinematics before and after the application of neural networks in comparison to an opto-electronic measurement approach.	**Aim II:** Develop a portable method to capture 3D movement	7
7	Virtual Rehabilitation vs. Physiotherapy: A comparison of two rehabilitation approached on hand function in patients with systemic sclerosis	Experimental study: RCT comparing the effect of two intervention programmes to improve hand function in patients with SSc	**Aim IV:** Examine the effect of the virtual rehabilitation tool in comparison to traditional physiotherapy on hand movement limitations	3, 4, 5, 6
8	General discussion			

Figure 4: Thesis structure outlining the chapter content and, where applicable, the structural design, addressed aims and interconnected chapters. This figure will be presented at the beginning of each chapter to guide the reader through the thesis.

Chapter 3: Describing the development of an opto-electronic and a markerless motion capture approach for the hand and subsequent kinematic modelling

Thesis structure				
Chapter	Title	Structural design	Addressed Aims	Linking to Chapters….
3	Describing the development of an opto-electronic and a markerless motion capture approach for the hand and subsequent kinematic modelling	Developmental study: Technical chapter outlining the design of kinematic models used in this thesis		4, 6 and 7
4	A comparison of hand movements during functional tasks in patients with systemic sclerosis and age- and hand dominance-matched healthy controls	Experimental study: Comparing hand movements of patients with SSc to age-matched healthy controls to quantify joint specific movement impairments	**Aim I:** Accurately assess the hand movement limitations of patients with SSc during functional tasks using three-dimensional motion analysis	5 and 7
6	Improving the accuracy of the Leap Motion controller for purposes of markerless hand motion capture using artificial neural networks	Experimental study: Assessment of the Leap Motion controller to accurately measure hand kinematics before and after the application of neural networks in comparison to an opto-electronic measurement approach.	**Aim II:** Develop a portable method to capture 3D movement	7
7	Virtual Rehabilitation vs. Physiotherapy: A comparison of two rehabilitation approached on hand function in patients with systemic sclerosis	Experimental study: RCT comparing the effect of two intervention programmes to improve hand function in patients with SSc	**Aim IV:** Examine the effect of the virtual rehabilitation tool in comparison to traditional physiotherapy on hand movement limitations	3, 4, 5, 6

3.1. Preface

Chapter 2 provided an overview of three-dimensional hand movement analysis with and without skin-mounted markers. Either method provides an objective evaluation of hand mobility, which could enhance knowledge gained from subjective patient-reported outcome measures. Both approaches (markerless and marker-based) to motion analysis have benefits and limitations which were highlighted in Chapter 2. Markerless motion capture is typically faster to apply and analyse, but it is prone to errors in the kinematic output variables. Skin mounted marker-based approaches require specialised software and cameras, making them typically more stationary and expensive, yet this approach is the gold-standard as this type of analysis is highly accurate.

Regardless of the data collection method, to calculate motion parameters, such as angles, velocities and accelerations, kinematic modelling is required. The type of model is based on the available motion data and can vary in complexity. The study design typically indicates the type of model required to fulfil the purpose for a research study. While one research study might desire highly accurate data without being concerned for time-demand, another one might require more portable methods which can be quickly analysed and converted into reports. Therefore, there is no 'one size fits all' kinematic model.

With an outlook onto the work presented in this thesis, the **aim** of this chapter is to describe two motion capture approaches and subsequent kinematic models.

3.2. Background

Quantitative, kinematic evaluation of hand movements using motion analysis can provide useful information for clinicians to improve diagnostics or assess the effectiveness of rehabilitation programmes following traumatic injury (Baker et al., 2016; Simon, 2004). Skeletal movement is assessed using various techniques. The most common method involves the placement of reflective markers on the skin surface. Placing reflective markers on each segment is challenging given the size of finger bones. To define a three-dimensional segment, three non-collinear markers on anatomical landmarks are required. The tracking of these markers in a calibrated space allows the determination of location of the markers in a local 3D coordinate system. Anatomical segments can then be defined based on a calibration trial. These segments are based on marker position in the originally calibrated space. Following calibration, each segment will have an orientation and position, which is reflected in the anatomical or segment specific coordinate system. In a final step joint centres or joint axis of rotation (AoR) are determined as the static point or axis about which rotational movement occurs between two adjacent segments. The skin around finger joints is very mobile increasing the soft-tissue artefact of markers placed close to the joint and thereby potentially inducing measurement errors (Lee and Jung, 2015; Ryu et al., 2006). Leap Motion Inc., a company to develop touchless interaction devices for computer users, created a highly advanced haptic device called the Leap Motion controller (LM). The LM includes two cameras capturing fingertip and palm positions relative to the device allowing the integrated algorithm to calculate joint centres. While this method can be applied easily, absolute joint centre positions are likely to be inaccurate, leading to incorrect joint angle calculations (Nizamis et al., 2018; Smeragliuolo et al., 2016).

The methods chosen to capture movement data is an important aspect to motion analysis. Yet the greater challenge is the accurate measurement of joint angles throughout the ROM, which requires a kinematic model. Kinematic hand models proposed in the current literature mostly assume the hand is a hierarchical kinematic chain of rigid bodies (Cerveri et al., 2007; Degeorges et al., 2005; Lee and Jung, 2015). For simplicity, the static IC joints and CMC joints of digits 2-5, are often grouped into a single segment (Cerveri et al., 2007; Lee and Jung, 2015). The remaining 15 joints (nine IP, five MCP, one TM joint) can then be linked to the rigid palm segment in a kinematic chain. None of the finger joints is a 6-Degrees of Freedom (DoF) joint. The MCP joints of digits 2-5 are bi-axial condyloid joints allowing movement over the flexion-extension (FE) axis and abduction-adduction (AA) axis (2 DoF joints) (Biggs and Horch, 1999; Cerveri et al., 2007; Coupier et al., 2016; Leitkam et al., 2015). The uni-axial IP joints and the MCP joint of the thumb are restricted to 1 DoF (FE axis) due to anatomical (hinge joint) constraints (Braido and Zhang, 2004; Coupier et al., 2016; Lee and Jung, 2015). The bi-axial TM saddle (2 DoF) joint allows three functional types of movement: flexion-extension, abduction-adduction and their combination termed circumduction (Carpinella et al., 2006; Domalain et al., 2011; Giurintano et al., 1995; Halilaj et al., 2014; Li and Tang, 2007). Circumduction is possible due to an interaction of flexion-extension and abduction-adduction ranges, therefore even bi-axial joints allow three functionally different types of movement.

Surface markers are tracked in a 3D Cartesian coordinate system reflecting their position within the capturing volume relative to a defined origin. Motion parameters, such as joint kinematics, are typically expressed in a segment specific 3D coordinate system as they describe the movement of two adjacent segments relative to one another. To define a segment coordinate system the location of the joint centre of rotation (CoR) and direction of the axis of rotation (AoR) is required (Wu et al., 2005). If surface markers are applied, substantial calculations and mathematical assumptions are required to identify both the CoR and AoR of the underlying bone morphology. Multiple mathematical models for these calculations have been proposed in the literature (Coupier et al., 2016; Leitkam et al., 2015; Ma'touq et al., 2018; Schwartz and Rozumalski, 2005; Zhang et al., 2003). A frequently applied algorithm to calculate the CoR (or functional joint centre) is the GILETTE algorithm (Schwartz and Rozumalski, 2005). This algorithm determines the CoR (for one or more DoF joints) or AoR (one DoF joints) by applying kinematic constraints and non-parametric statistics. The movement between two segments proximal and distal to a single joint is evaluated to determine the AoR. The CoR (only in the presence of movement across at least two DoF) can then be determined as the intersection of the AoRs in any position, thus reflecting a static point of movement between the two segments (Schwartz and Rozumalski, 2005). The LM provides CoRs for all joints, but it remains unknown how exactly the integrated algorithm computes the joint centre data from the video images. Similar to the different data acquisition methods (marker-based or markerless), different approaches to determining AoR or CoRs exist, which presumably rely on distinct mathematical assumptions made.

There is no standardised model for hand movements. All proposed models in the literature have advantages and disadvantages linked to the complexity of the marker setup, definition of joint coordinate systems or the extend of skin motion artefact. The wide range of models enables researchers to choose models based on study needs. For highly accurate tracking of bone morphology and joint movements, more complex, marker-based motion capture principles with many cameras may be useful. However, this approach is unlikely to be translatable into clinical practice or real-time applications (Cerveri et al., 2007), which value fast processing methods and user-friendliness even at the expense of lower accuracy. To meet the demand of the work conducted for this thesis, two motion capture approaches and associated hand models were generated to calculate joint kinematics of the TM, MCP and IP joints of all digits during dynamic tasks.

3.3. Development

3.3.1. Marker based motion capture

Non-invasive skin surface marker-based motion capture was used to define pathological hand movement limitations in patients with SSc. To accurately determine kinematic profiles and their deviations from normality during functional tasks, a complex marker model was generated (3 DoF), which allowed the computation of functional joint centres using the GILETTE algorithm or, where required, anatomical markers.

3.3.1.1. Marker arrangement and labelling

Reflective markers where arranged in sixteen clusters with three spherical markers (Ø 3 mm) each (48 markers in total) (Figure 5a). The clusters were ergonomically shaped to match the underlying bone morphology and attached to the dorsum of the hand. Four cluster sizes were created with dimensions 10 mm x 8 mm (length x width), 12 mm x 10 mm, 14 mm x 11 mm and 16 mm x 12 mm. The use of multiple cluster sizes enabled the researcher to match the marker setup to individual hand dimensions. The marker setup has been used in previous researched published in the literature to measure grasping movements (Lee and Jung, 2016). Cluster arrangements enhance the ease of application, and are thought to reduce potential measurement errors induced by the soft-tissue artefact (Houck et al., 2004). To ease labelling the clusters were eventually rotated clockwise 90° for the index finger, 180° for the middle finger and 270° for the ring finger. Whilst the use of three markers per segment is unnecessary to track motion of the hinge joints (1 DoF), it increases the accuracy of the initial functional joint calibration. If movement range was sufficient, a functional movement trial was recorded. The movements tracked were: TM joint flexion-extension, abduction-adduction and circumduction, flexion-extension and abduction-adduction of the MCP joints of digits 2-5, and flexion-extension of the IP joints and thumb MCP joint. If movement limitations were severe in pathologic participants, 30 skin-mounted markers (Ø 2 mm) were applied for a static calibration trial (Figure 5b) only.

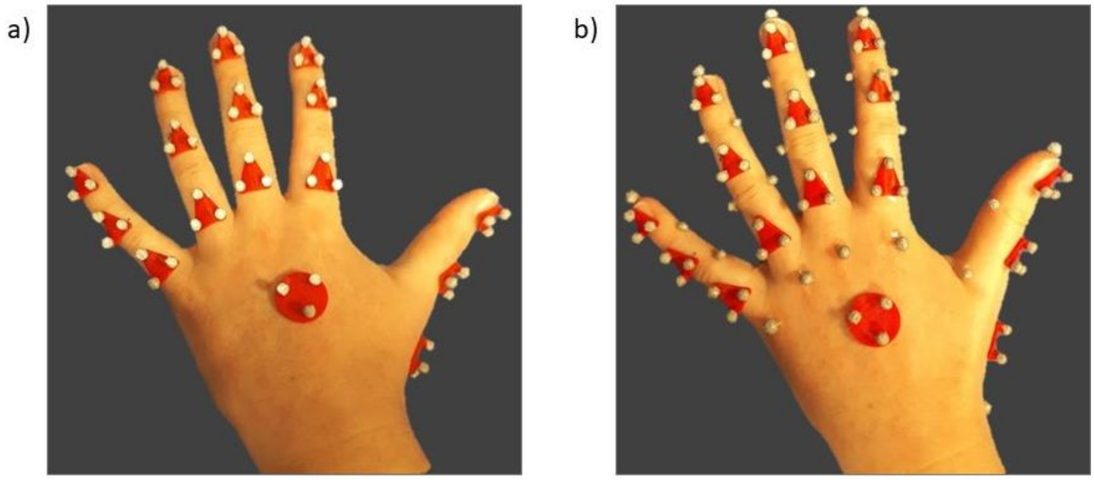

Figure 5: Reflective markers were applied to the dorsum of the hand to track movement of the long finger bones. a) 48 markers arranged in 16 clusters to track the 16 mobile segments. b) If functional ROM was insufficient in pathological participants, 30 anatomical markers were applied: one on the fingertip, one dorsal to the MCP joint of digits 2-5, one dorsal to the TM joint and one medial and lateral to the IP joints and thumb MCP joint.

3.3.1.2. Visual3D modelling

A calibration model was generated from a static trial. AoR or CoR for each joint were computed using the GILETTE algorithm. All 1 DoF joints (IP joints and the thumb MCP joint) were computed as functional axis (AoR) with the second landmark offset by 1 cm, which reflects the FE axis. The functional axis has no anatomically linked direction and could point medially or laterally to the segment, thus affecting the orientation of the segment coordinate system and requiring potential manual adjustments. Neither of the two axis points calculated by the GILETTE algorithm reflects the joint centre, however, the joint centre does lie on the infinite axis passing through these two calculated points. Therefore, a joint centre landmark (JC_Finger_Joint) was created if a joint was defined as functional axis (Figure 6a). This landmark was created in two steps: First the central cluster axis was defined, and a landmark (J_Projection, whereby J was replaced by the joint of concern) was projected from the joint axis marker onto the central cluster axis. In a second step the joint centre was defined on the functional axis using the

a) b)

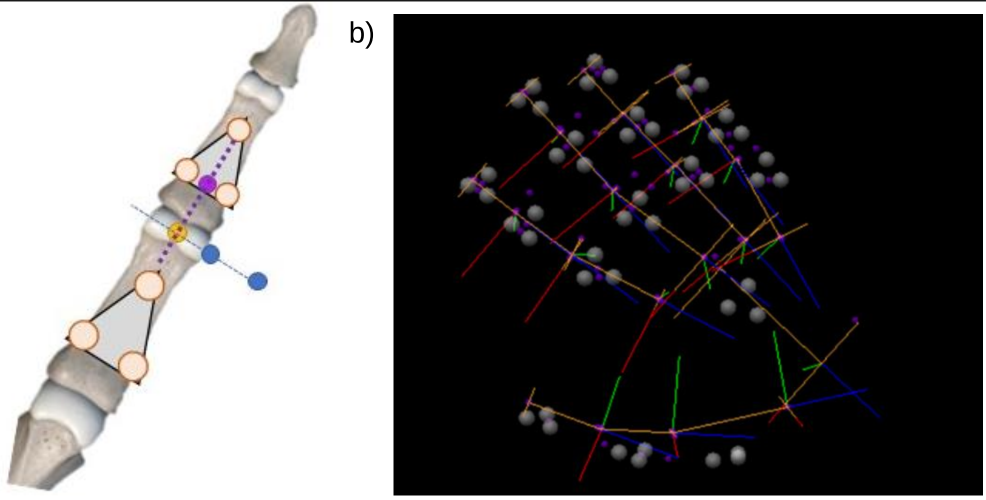

Figure 6: Location of CoR and AoR was computed using the GILETTE algorithm. a) where computed as an AoR, the joint centre (yellow) was determined at the intersection between AoR (blue) and central cluster axis (purple) from the distal segment of the joint. b) Segments were created and the segment coordinate system at the joint centre proximal to the bone.

J_Projection defined in a previous step as a lateral object. Therefore, the joint centre landmark was on the functional axis calculated by the GILETTE algorithm, at the point where the central cluster would cross at an offset. As the cluster was placed centrally on each phalanx the central cluster axis should point at the joint centre on the functional joint centre axis (Figure 6a). The MCP joints of digits 2-5 and the TM joint were computed as a point, or CoR, as these joints allow 2 DoF movement. Accurate computation of functional axis or joint centres requires approximately 20° ROM. If the movement in a joint was insufficient (less than <20° ROM) to calculate a functional joint centre/axis using the GILETTE algorithm anatomical markers were used to determine the joint centre for that specific joint. Anatomical markers were placed medially and laterally to each joint on the axis of rotation. The CoR was estimated to be the mid-distance point between the two anatomical joint markers (C-Motion, 2017).

Following the identification of joint centres, kinematic only segments were created using the computed CoRs or AoRs as proximal and distal end points. Sixteen segments were defined: the palm (1x), all phalanges (14x) and the thumb metacarpal (1x). The segments were defined from proximal to distal joint, with the third marker being the first functional axis marker, and the cluster markers as tracking targets (Figure 6b).

Last, segment constraints were defined using the inverse kinematic model algorithm in Visual3D (C-Motion, Germantown, WD, USA). The palm is free moving relative to the lab (6 DoF). Movement across the MCP joints of digits 2-5 and the Thumb TM joint was restricted to rotations in the sagittal and frontal plane (2 DoF). The movement of IP joints and the thumb MCP joint was restricted to rotation in the sagittal plane (1 DoF).

3.3.2. Markerless motion capture

The LM with two cameras, three infrared LEDs (Figure 7) and its integrated algorithm calculates a hand skeleton including joint centres from fingertip and palm positions relative to the device without any marker placement on the skin. Additionally, it is portable and easy to use with any laptop. The LM is very user friendly, however for use as a motion capture device a link to a third-party software needs to be designed which is described below.

Figure 7: Technical setup of the Leap Motion controller. The sensor is 7.6 x 3 x 1.3 cm (length x width x height), weights 45 grams and includes two wide angle cameras (yellow), three infrared LEDS (blue) and computing space for the integrated algorithm. Image adapted from Leap Motion Inc. (Colgan, 2014).

3.3.2.1. Extracting Joint Centre coordinates and establishing a data stream

A computer program was written in C# (Visual Studio 2015, Microsoft Corporation, Redmond, WA, USA) to extract 3D joint coordinates from the LM sensor and stream them into D-Flow (Motekforce Link, Amsterdam, The Netherlands) for data collection. Frame number, frames per second, time stamp and hand count were assessed for each data frame captured by the LM. If hand count was equal to one, a series of loops was initiated. These loops defined the position and direction of the palm, hand and finger identity, length and width. The LM software developer kit (SDK) provided insight into the definition of the bone segments within the finger. If all five digits were identified a nested loop would define individual bone (finger.bone) orientation, which is defined by the proximal joint (bone.PrevJoint) and distal joint (bone.NextJoint). The joint coordinates of the proximal and distal joints were then stored in a matrix, and plotted on a chart (Figure 8a). The loop was inactive if the LM was disconnected or no or more than one hand was present above the sensor (hand count ≠ 1). A network data stream through the public string IP address was established between the C# program and D-Flow following company instructions (MotekMedical, 2016). The 3D coordinates of joint centres and fingertips were streamed as 75 data points from LM to D-Flow upon initiation of the connection. The connection between D-Flow and LM was initiated by

a) b)

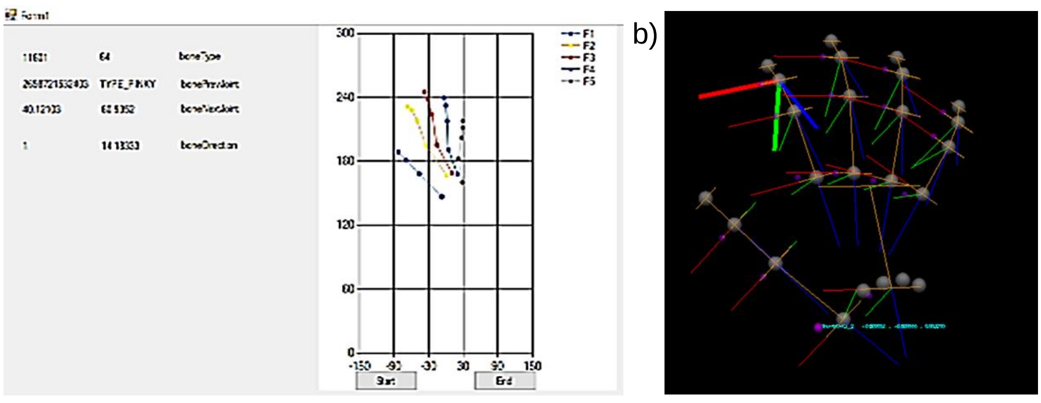

Figure 8: Hand movements were recorded using the Leap Motion and streamed to D-Flow (Motekforce Link) using a the C# program, which was used to visually assess quality and to initiate/ terminate the data stream (a). The data was then modelled in Visual3D (C-Motion Inc.) to generate segments and kinematic output variables (b).

the activation of the Network Module in D-Flow, followed by the activation of the C# program. The stream was terminated by either deactivation of the C# program or the Network Module in D-Flow. As the LM reports in mm, the integers were divided by 1000 to scale to D-Flow units (m). The Network Module was set to act as server, with two clients (D-Flow and LM), three server channels (default setting), and 75 client channels, which is equivalent to 3D coordinates of the 20 joint centres (the TM joint is registered twice) and five fingertips extracted from the LM software. The three-dimensional coordinates were visualised in D-Flow to assess the quality of data captured. The recorded 3D coordinate data of the LM joint centres was exported as text file.

3.3.2.2. Visual3D modelling

Extracted data was stored in a tab-delimited text file and converted into a c3d file using Visual3D (C-Motion, Inc., Germantown, MD, USA) prior to modelling. A static calibration trial was used. As joint centre coordinates are already present, no further computation using the GILETTE algorithm is required. Joint centre coordinates for the CMC (including the TM), MCP, and IP joints as well as fingertips (24 targets) were measured in the local LM coordinate system (attached to the LM device), and 16 segments (palm (1x), all phalangeal bones (14x), thumb metacarpal (1x)) were defined. As the definition of a 3D segment requires the presence of three markers, a landmark was generated 1 cm medial to the TM, MCP and IP joints. Therefore, hand position was standardised in the lab with the palm parallel to the LM controller. Bone segments were defined from proximal to distal joint centre coordinates as measured by the LM, whereby the tip reflected the distal end point of the distal phalanx. As a third marker the landmark generated medially to the proximal joint of each segment was used. All segments were created for kinematics only. The palm was defined using the TM and little CMC joint on the proximal end and the index and little MCP joint on the distal end (Figure 8b).

3.4. Evaluation

Two models to calculate joint kinematic parameters at the TM, MCP and IP joints of the hand were created. Both models include the creation of 16 segments in a kinematic rigid-body chain. The palm acts as the root segment for the fingers. The models allow the calculation of angular displacement, angular velocity and angular acceleration in the constrained planes. Joint kinematics are expressed in the local joint coordinate system of the proximal joint. Kinematics are determined by assessing the movement of the distal segment in the coordinate system of the proximal segment, effectively representing the movement between two adjacent segments. The IP and thumb MCP joints are constrained to flexion-extension movement only (X-axis rotation), while the MCP joints of digits 2-5 and the TM joint are allowing flexion-extension and abduction-adduction (X- and Y-axis rotation). The orientation of the joint coordinate systems is similar between the models. The X-axis (red) represents the flexion-extension movement, while the Y-axis reflects abduction-adduction range (green). The longitudinal Z-axis (blue) reflects rotation in the transverse plane, which is irrelevant for the hand movements owing to the anatomical constraints of the skeleton. Each model can be applied bilaterally by negating abduction-adduction kinematics of one hand when comparing left- and right-hand movements. The definition of segments and joint centres is individual to each model. The model using skin mounted markers central to the segment specified relies on mathematical assumptions from the GILETTE algorithm to determine the functional axis. To determine the actual joint centre location, the assumption was made that the central cluster axis is pointing to the joint centre following accurate marker placement. If clusters were placed inaccurately or by an unpractised researcher this may lead to substantial errors, which would lead to wrongful definition of segments and thus inaccurate calculations of joint kinematics. The LM model, or markerless approach, is based on joint centres determined by the

Table 2: Summary of the advantages and disadvantages of the respective motion capture approaches and subsequent kinematic modelling outlined in this chapter. The benefits and limitations under consideration of a research design influence the model type which fulfils the requirement for a specific study.

	Leap Motion data acquisition and model	**Skin-surface mounted marker data acquisition and model**
Pro	• Portable equipment • Cheap • Easy to use • Fast data collection • Short processing time • LM software for visualisation of data great demo tool when showing participants what will happen in the study and what kind of data is collected.	• Accurate • Responsive to deformities • Systems have been validated vigorously • No standardised position within the calibrated 3D space required for modelling
Con	• Less accurate • Relies on mathematical assumptions which cannot be accessed • Offset of horizontal landmark only works during standardised position • Uncertain responsiveness to hand deformities	• Stationary and lab based • Expensive • Expertise required to use the system • Slow processing time • Data collection duration is longer due to the placing of markers on the skin

LM algorithm. While it is likely that the method for this relies on interpolation methods, it is not entirely determinable what mathematical assumptions have been made to create the algorithm. The creation of landmarks at an offset in Visual3D is based on the assumption of a standardised position relative to the device, which was established using a wrist support structure. However, small changes in position if a subject would not follow instructions, could lead to large errors in the determination of the joint axis and therefore kinematics. Both models rely on mathematical assumptions of which some can be controlled by the researcher. Given the difficulty to access the algorithm which creates the joint centres for the LM, it might be easier to influence and manipulate the skin-mounted marker model. Calibration of joint centres from surface markers is however time consuming and requires training, whereas the LM model can be applied quickly for fast analysis.

3.5. Application of the methods to research

The purpose of a research study significantly influences the design of the model used to generate the desired output parameters. While both models created in this thesis may calculate the same kinematic parameters, there will be differences in magnitude of these parameters between the models (Lee and Jung, 2015). As in the lower extremity, different models will generate slightly different magnitudes for the same parameter (Collins et al., 2009; Houck et al., 2004; Lee and Jung, 2015). Therefore, for one study only one model can be applied to compare multiple individuals or change over time.

The marker-based motion capture model might be the most accurate and most responsive to bone deformities (Leijnse et al., 2010), while it is uncertain how responsive the LM is to hand deformities. Marker-based motion capture and modelling is thought to describe pathological movement more accurately, as it reduces the number of mathematical assumptions when compared to an algorithm and subsequent modelling.

The application of markers and processing of the collected data is highly time consuming and requires expertise. Accurate marker placement is essential as the definition of joint centres relies on the cluster being accurately placed in the centre of each segment, and a slight inaccuracy can induce sizeable measurement errors (Gorton et al., 2009; Groen et al., 2012; Kadaba et al., 1989; Schwartz et al., 2004). Calculating multiple functional joints further increases the time demand. Therefore, whilst this model is accurate, it is not readily applied in clinical practice. The LM joint centres can be easily extracted once the software is set up, and modelling only requires minimal time. Hence this model fulfils the requirements for an easy and quick to use model to calculate joint kinematics. However, it is based on data from an algorithm, which itself cannot be accessed. The data from the LM is insufficient to create a 3D segment, therefore a third, virtual landmark is required as previously described. The effect of an inaccurately determined virtual landmark could be detrimental (Groen et al., 2012; Kadaba et al., 1989; Schwartz et al., 2004). However, the effect of virtual landmark position relative to the measured joint centres was not quantified in this thesis. To minimise the potential error in this research project, the hand position was standardised to a parallel position of the palm relative to the LM. This position was easy to control using a support structure to guide hand position. Given a standardised position the error would have been the same across all participants.

While both models have certain benefits and limitations, it is important to acknowledge that none of these models have been validated using MRI or dynamic videogrammetry fluoroscopy scans. Modelling of the hand is a challenging task considering the anatomical and neural constraints of the joints as well as segment size. When applying reflective markers to the dorsum of the hand most movements can be tracked, but upon full flexion the camera view of the distal phalangeal bones will be obstructed by the hand itself. This limits the use of marker-based motion capture for full flexion tasks. The LM does not allow fingers to be completely straight, thus full extension cannot be measured in healthy individuals, limiting the LM ability for motion analysis.

3.6. Summary

Two models for the calculation of finger joint kinematics were generated. These models differ in complexity, accuracy and user-friendliness. This research thesis outlines highly technical studies, but also aims to produce translatable research for clinical applications, therefore there is a demand for models with different capabilities. The developed models were deployed to meet the specific experimental needs of each study, to allow the conduction of both technical and translatable hand movement research. The marker-based model was applied in laboratory-based test protocols (Chapter 4) and as a reference to improve the kinematic data from the markerless motion capture approach (Chapter 6). The LM based model was applied in a home-based intervention study with patients (Chapter 7).

Chapter 4: A comparison of hand movements during functional tasks in patients with systemic sclerosis and age- and hand dominance-matched healthy controls

Thesis structure				
Chapter	Title	Structural design	Addressed Aims	Linking to Chapters….
3	Describing the development of an opto-electronic and a markerless motion capture approach for the hand and subsequent kinematic modelling	Developmental study: Technical chapter outlining the design of kinematic models used in this thesis		4, 6 and 7
4	A comparison of hand movements during functional tasks in patients with systemic sclerosis and age- and hand dominance-matched healthy controls	Experimental study: Comparing hand movements of patients with SSc to age-matched healthy controls to quantify joint specific movement impairments	**Aim I:** Accurately assess the hand movement limitations of patients with SSc during functional tasks using three-dimensional motion analysis	5 and 7
5	Method chapter: Design of a virtual rehabilitation game for systemic sclerosis informed by three-dimensional movement analysis	Developmental study: Technical chapter with a detailed description of the design of a virtual rehabilitation tool for patients with SSc	**Aim III:** Deploy the portable motion capture method into a virtual rehabilitation context	7
7	Virtual Rehabilitation vs. Physiotherapy: A comparison of two rehabilitation approached on hand function in patients with systemic sclerosis	Experimental study: RCT comparing the effect of two intervention programmes to improve hand function in patients with SSc	**Aim IV:** Examine the effect of the virtual rehabilitation tool in comparison to traditional physiotherapy on hand movement limitations	3, 4, 5, 6

4.1. Preface

Chapter 3 described the design of an accurate reflective marker-based approach to hand movement analysis, which can determine hand kinematics in all degrees of freedom of a given joint.

Comparing results of patients against those of healthy controls is common for a wide range of clinical tests, such as blood tests, to determine if a patient falls outside of a normal range, and by how much. The extent of elevated or reduced level of the assessed parameter then influences treatment options. For movement, indices have been developed for the lower extremity to determine the difference between impaired and non-impaired movement profiles. These indices are mathematically translatable to the upper extremity and hand. Hand movements are known to be impaired in patients with SSc, yet joint specific impairments have not been assessed, nor have patterns of movement limitations been evaluated.

The **aim** of this study was to accurately determine hand movement limitations in patients with SSc by calculating the deviation from normality as defined by an age- and handedness matched healthy control cohort during functional tasks. A second aim was to identify the extend of contribution of individual joints or degrees of freedom to the overall hand impairment. This is achieved by applying the Movement Deviation Profile (MDP) to determine 1) overall movement impairment of the whole hand and 2) joint specific contribution to the overall impairment by eliminating a single joint at a time from the analysis. It is hypothesised that patients will show a significant overall impairment compared to healthy controls throughout the movement phase. Further it is hypothesised that some joints will have a greater contribution to the overall impairment than other joints, which will be identified by eliminating a single joint at a time from the MDP analysis. As the work in this thesis aims to be translatable to clinical practice a correlation of the MDP_{mean} to simple clinical measures is will be done to identify a single or combination of numerical clinical measures which could be used to predict movement impairment in clinical practice. It is hypothesised that at least one measure or combination of measures correlates strongly with the MDP_{mean}. The knowledge acquired in this chapter informed the design of a novel intervention tool (Chapter 5).

4.2. Introduction

Hand movements are commonly impaired in SSc patients as an increase of collagen fibres in the skin leads to increased thickness and stiffness. This loss in hand mobility, amplified by calcium deposits, digital ulceration and Raynaud's phenomenon (Yamamoto, 2009), is associated with a reduced ability to perform ADLs, such as getting dressed, eating and drinking, and therefore a reduced quality of life (Maddali-Bongi et al., 2014; Mao and Sun, 2014; Nguyen et al., 2014).

As discussed in the literature review (see Chapter 2) the current assessment methods for hand mobility are subjective, and thus objective measures are required to inform clinical decision making and rehabilitation programmes. Based on subjective, patient reported questionnaires it has become apparent that patients with SSc struggle with a wide range of tasks, predominantly with picking up small items (pulp pinch) and unscrewing lids (extension grip), but these reported problems have yet to be quantified objectively.

Gait analysis is a validated assessment tool to objectively measure lower extremity movement impairments in clinical populations. Assessing movement parameters, such as kinematics and kinetics, provides new information about a patient's movement impairment to support clinical decision making and treatment options (Konig et al., 2016; Lofterod et al., 2007). The use of 3D motion analysis is however not limited to the lower extremity. In prior research, movement analysis of the hand has been used to determine healthy motion patterns of various ages, as well as during functional tasks, gestic acts and dexterity skills (Agnew and Maas, 1982; Braido and Zhang, 2004; Coupier et al., 2016). A 3D motion analysis of movement limitations in SSc patients could therefore provide the objectivity that current assessment tools lack.

Movement data, in the form of movement curves throughout a specific motion, is multi-dimensional and difficult to understand. As the hand is a highly complex, kinematic chain, every kinematic measure is simultaneously affected by, and affects itself, the movement of the adjacent and even further joints. To aid the understanding of complex data discrete values are determined, such as maximum flexion and extension angles, and range of motion. However, as movement is continuous, the selective approach to evaluate peak and trough values induces bias and ignores potentially important time-dependent movement impairments (Baker et al., 2009). Currently there is insufficient information on hand kinematics to deduce which discrete values are important to overall hand function. Given the kinetic and kinematic chains of the hand one impaired joint would subsequently affect the recorded impairment in adjacent joints and thereby skew the results of a joint-by-joint analysis approach, such as used in statistical parametric mapping (SPM) (Pataky, 2010) or when comparing discrete measures using an ANOVA or MANCOVA analysis, suggesting that this type of analysis as limited potential for hand function. Movement analysis yields a large amount of data. To reduce the amount of data while retaining most of the information contained in temporal movement curves, indices were developed to summarise the movement impairments of patients (Baker et al., 2009; Barton et al., 2012; Schutte et al., 2000; Schwartz and Rozumalski, 2008; Wren et al., 2007). The use of indices increases the use of gait analysis in clinical applications, but also helps to understand disease progression and severity. While several gait indices exist, no index has been used for the evaluation of hand movement limitations, despite most being theoretically mathematically translatable to the upper extremity. The common indices used in gait analysis are the Gillette Gait Index (GGI) (Schutte et al., 2000), Gait Deviation Index (GDI) (Schwartz and Rozumalski, 2008) and the Gait Profile Score (GPS) (Baker et al., 2009). The GDI (Schutte et al., 2000) is based on discrete variables, which are known to be linked to overall impairment of the lower extremity. Given that this data does not exist for the hand, the use of the GDI is inappropriate at the current time. The GDI (Schwartz and Rozumalski, 2008) and GPS (Baker et al. 2009) both consider the movement curves of established kinematic variables of impairment, and compare the patient to the mean of a healthy control. The resulting data is a single number which indicates average level of impairment in relative terms throughout the movement phase. There are however two significant issues: firstly, comparing patient data to a mean value could be considered incorrect as normal or healthy is typically a range of values. Therefore, comparing a patient to a mean value could overestimate the actual level of impairment. Comparing to the end points of the range would therefore be a better choice. Secondly, the level of impairment is summarised with no indication at which time throughout the dynamic task at hand the patient shows greater or lower levels impairment. In the hand this would be linked to reaching, grasping or releasing phases of the movement. In the current literature it is unknown if patients with SSc are more limited in certain phases of movement, which would be vital to know for later rehabilitation and intervention protocols. Therefore, both the GDI and GPS, whilst translatable and applicable, do not provide the information that would be required for a summative hand index at the current state of knowledge of hand function. Another gait index is the movement deviation profile (MDP) (Barton et al., 2012), a single curve describing the multi-dimensional distance between abnormal patient movement and typical, healthy movement. The MDP is based on Kohonen's self-organising map (Kohonen, 1981), a form of artificial intelligence. A self-organising map (SOM) is trained using unsupervised learning. The process of a SOM consists of two stages: training and mapping. The training phase builds the map using input training vectors, for example healthy movement data. The training phase relies on vector quantisation. Prior to training the neurons of a SOM are arranged in a two-dimensional sheet, with a 'weight vector' attached to each neuron which determines the connection strength of each neuron to the input space. During the training the distance between input vector and weight vectors is reduced, thus the neurons form a map space reflecting the range of input data that it was given during training. The map is usually defined as a two-dimensional surface, but it can be trained with multi-dimensional inputs, allowing the visualisation of multi-dimensional input data in a 2D map following dimension reduction.

Once training has been completed, the mapping stage allows a SOM to evaluate a new data vector, for example a vector of pathologically impaired movement, and find the neuron with the closest matching weight vector. Therefore subsequent to training a SOM with a range of normal movement data, the deviation of abnormal movement from normality can be quantified by calculating the distance between the abnormal input vector (pathological hand movement) and the closest matching weight vector (based on non-pathologic movement data) in the multi-dimensional space (Barton et al., 2006; Barton et al., 2012). This calculation is done for every time point of the set of movement curves, resulting in a single curve that describes the deviation from normality throughout the entire movement phase. The mean of the MDP curve (MDP_{mean}) can be calculated to effectively summarise the motion analysis outcome to a single value. Whilst originally developed for gait, the MDP method can be used for any multi-channel, temporal data set (Barton et al., 2012), including hand kinematics.

Evidence-based clinical practice requires reliable data, and patient-reported outcome measures are known to be influenced by psychological factors, such as outlined in the Kübler-Ross model (Bolden, 2007). Further, patient-reported outcome measures do not provide a comparison to normal data, yet, normal needs to be defined in order to understand and correctly interpret abnormal patient data (Charan and Saxena, 2012; Page, 2014). Using normal reference values is common practice in clinical tests, such as blood tests, as without the normal range a clinician would not be able to identify if, for example, blood sugar or inflammatory factors are too high. The same concept applies to movement. No two people will ever move exactly the same, therefore a distribution or range of normality needs to be defined to which patients can be compared to. The comparison of patients to a spectrum of healthy controls then enables clinicians and researchers to intervene with the movement impairments in an evidence-based approach. The aim of this study was to objectively quantify overall and joint specific contribution to hand movement deviation from normality in patients with

SSc during two frequently affected functional tasks and to compare this objective measure to current clinical measures of hand function.

4.3. Methods

Ten patients diagnosed with SSc (ACR/EULAR score >9, without longstanding flexion contractures, 61 ± 15.6 yrs, all right-handed females) and eleven healthy controls (58.3 ± 14 yrs, 10 females, 2 males, all right-handed) volunteered to participate in this study. The National Health Service Research Ethics Committee and the Health Research Authority approved this study (IRAS: 218984, REC reference: 17/LO/0321). All participants provided written consent.

4.3.1. Protocol and data processing

The participants attended the research institute for a single session, where a motion analysis was conducted. For patients the time since diagnosis with SSc (disease duration) and FTP index were obtained. Reflective markers were placed on the dorsum of the dominant hand. Two functional tasks were performed using the dominant hand only: opening a 1) zipper (1.8 cm handle) (pulp pinch) and 2) large lid (Ø 10.5 cm) (spherical grip). The participants received no instructions how to complete the task, therefore every person could use their individual movement pattern. The distance between initial hand position and object (reaching distance prior to task execution) was standardised to 25 cm and the shoulder flexion angle prior to movement onset was standardised to 45° (Figure 9). Movements were captured and processed using 15 Vicon MX cameras (eight T160 and seven T10) and Vicon Nexus 2.5 software (Vicon Motion Systems Ltd, Oxford, UK). Joint angles were computed in Visual3D (C-Motion, Inc., Germantown, MD, USA). Owing to the anatomical and neural constraints of the hand only flexion-extension movements of all joints and abduction-adduction movements of the MCP joints of digits 2-5 and the TM joint (20 angular displacement

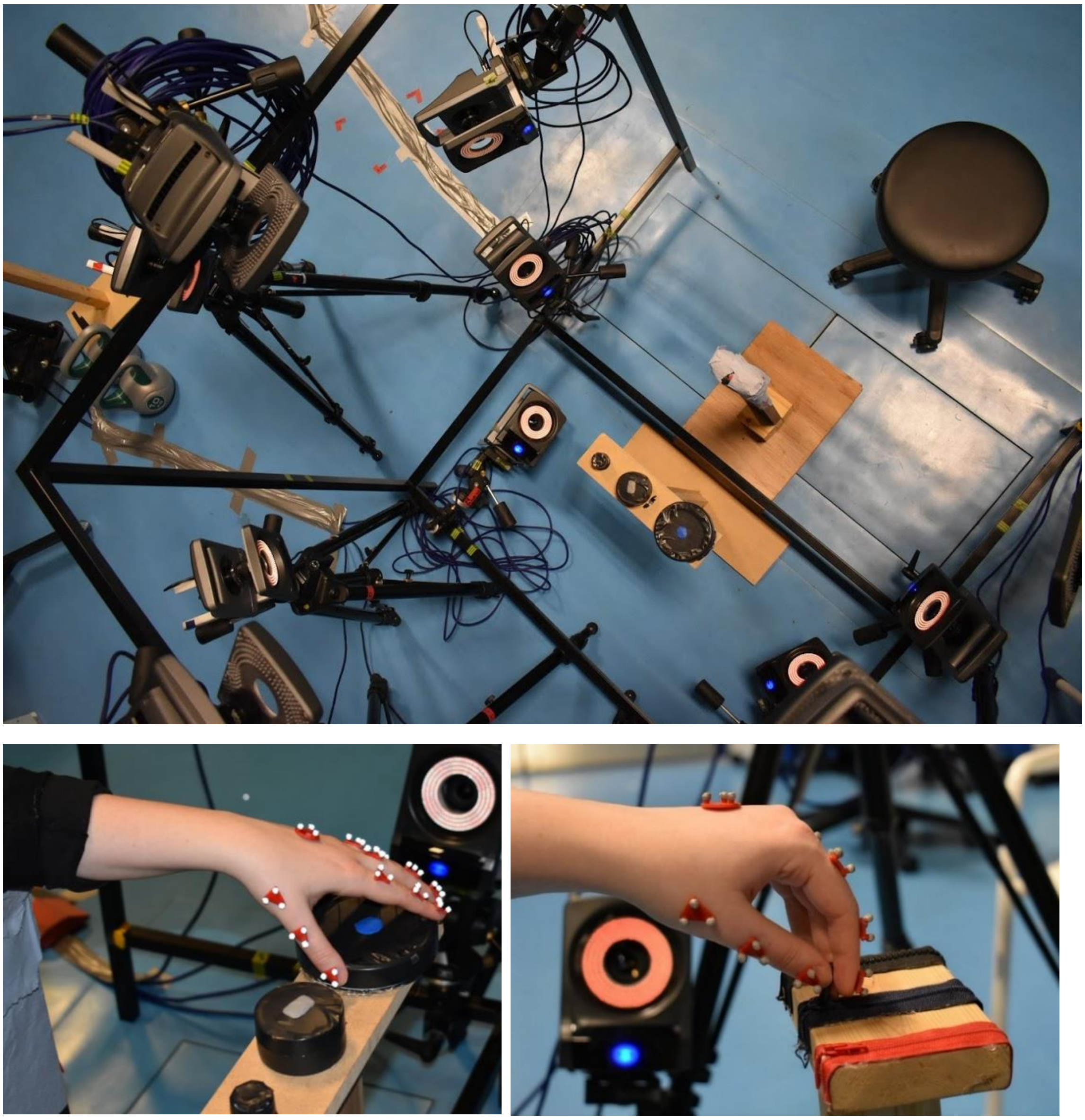

Figure 9: Lids and zippers were placed in the centre of a camera cube with a wrist support 25 cm away to standardise reaching distance from resting position to object. Participants sat on a height adjustable swivel chair to ensure a shoulder flexion angle of 45° prior to onset of movement. The tasks involved: reaching for the lid/zip, opening the lid/zip and closing it again before moving the hand back into a relaxed position with the wrist resting on the customised support structure.

curves) were considered in this analysis. The maximum extension angle (MEA) for all joints was determined during a maximum voluntary extension movement. The mean MEA (MEA_{mean}) was then calculated as the mean of all previously determined MEAs. Further movement time, defined from onset of movement to grasp completion, was acquired for every completed trial. Movement was further observed and described subjectively by the researcher. Inability of a patient to perform either task was notes for consideration in the analysis.

4.3.2. Movement Deviation Profile

A combined database for all healthy participants was generated for both functional tasks separately, including 20 angles of 36 recorded movements which were time normalised to 100 frames. The MDP and MDP_{mean} were calculated for each patient from onset of movement to grasp completion. The MDP is a single curve indicating deviation from normality throughout the movement, whereas the MDP_{mean} is the average of all points on the MDP curve (Figure 10), therefore summarising the deviation from normality into a single value. After initial overall MDP calculation, one joint angle at a time was left out to identify the contribution of individual joints to overall hand movement impairment (Barton et al., 2019). If the MDP_{mean} increased in the absence of a joint, the joint reduced the deviation from normality, making it less impaired than other joints. Conversely, if the MDP_{mean} decreased after a joint was eliminated from the calculation, indicating less deviation from normality, the eliminated joint is thought to have greater impairments leading to on average greater deviations from normality. A z-score transformation was performed to allow the determination of joint contribution relative to a standardised healthy control mean. For joint specific analysis all MDP_{mean} values are therefore expressed as z-scores.

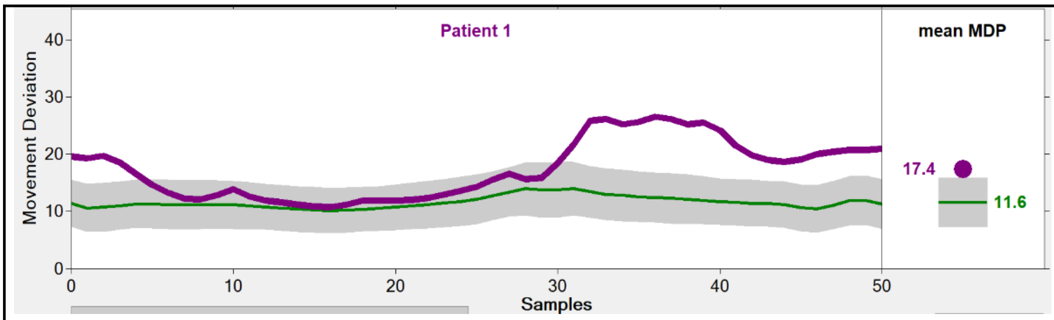

Figure 10: Example of a Movement Deviation Profile curve and MDP_{mean}. The healthy control data shows in green against the patient data (purple). The deviation from normality is the distance between the purple and green lines. Image generated using the Movement Deviation Profile programme by Gabor J. Barton (2009).

4.3.4. Statistical analysis

An independent samples 2-tailed Student's t-test was performed for the movement duration between the control and patient group to test if patients showed a significantly longer movement time compared to controls. The overall and joint specific MDP_{mean} was tested for significance using Student's t-test to test if patients showed a significant deviation from the normal, healthy movement patterns. Multiple correlations were conducted between the MDP_{mean} and clinical data, to identify if the level of impairment could be related to simple measures from clinical practice, thereby increasing the translatability of the index into clinical practice. Parameters included in this correlation were years since diagnosis, movement duration, MEA_{mean} and the FTP. The Pearson's correlation coefficient (r) was tested for significance (*p*) and the coefficient of determination (r^2) was calculated. A multiple regression analysis was performed to assess the multidimensional interaction between the MDP_{mean} and clinical measures of movement impairment, and tested for significance. All significance tests were tested against the null hypothesis (no difference between variables/ no interaction between variables). At an α-value of less than 0.05 the null hypothesis was rejected, and the alternative hypothesis (significant difference between variables/ significant interaction between variables) was accepted.

4.4. Results

Patients with SSc required significantly longer to complete both functional tasks compared to healthy controls (Figure 11). While some patients were still able to close their hand into a fist (n = 4, FTP = 0), no participant could extend the fingers into a fully flat hand, or slightly overextend the MCP joints (all participants $MEA_{mean} > 0°$) (Table 3).

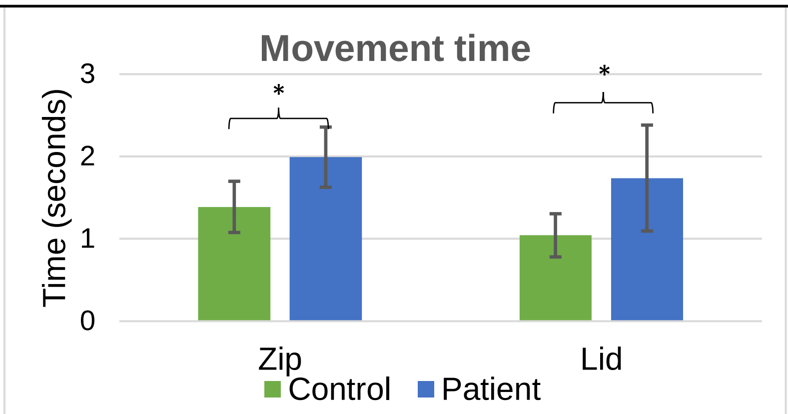

Figure 11: Patients with systemic sclerosis (blue) required significantly longer to complete both tested ADLs (Zip: $p = 0.001$; Lid: $p = 0.025$) than healthy, unimpaired individuals (green). Data shown as mean ± 1SD.

Table 3: Finger to palm index (FTP), mean maximum extension angle (MEA_{mean}) and disease duration for patients with systemic sclerosis.

	Mean ± SD	Range
FTP	0.81 cm ± 0.81	0 cm – 2.3 cm
MEA_{mean}	9.62° ± 7.51	1.97° – 27.36°
Disease duration	4.94 yrs ± 2.81	1 yrs – 9.5 yrs

4.4.1. Observed movement patterns

All patients were able to unscrew the lid by either using the palm to increase surface contact area with the lid to allow greater force production, or by generating a downward force on the lid through the fingertips to avoid slipping. No patient was able to stretch the fingers around the lid as non-pathologic individuals did. Healthy control participants unscrewed the lid by a gentle wrist motion, while patient participants required movement of the entire upper extremity to bring about a turning movement. All but one patient with systemic sclerosis were able to open the zip using adaptive mechanisms. These included a lateral pinch of the zip between thumb and index finger, pulp pinch between thumb and middle finger or clenching the entire hand around the zip. All healthy control participants pulp pinched the zip between the thumb and index finger and opened the zip by extending the wrist. Variations were observed for the movement of the little finger. While some healthy control participants extended the little finger when pinching the zip, others kept them in a flexed position. This underlines the large movement variability of the hand and the individuality of hand movement. Patient participants required movement in the entire upper extremity to open the zip, and showed stiff wrists.

4.4.2. Movement deviation profile

In both tasks, patients showed large and irregular deviations from normality throughout the entire movement phase (Figure 12). The differences in movement patterns between healthy controls and patients described above (section 4.3.1.) resulted in a significant deviation from normality for every patient participant when considering whole hand movements (raw MDP_{mean} Zip: Average: 50.3° ± 7.7, Range: 38.1°-65.3°; MDP_{mean} Lid: Average: 48.5° ± 8.8, Range: 31.2°-64.9°) (all MDP_{mean} $p<0.05$) (Figure 13). When examining the MDP curves of both tasks clusters of patient data can be identified. For the zip task, two clusters can be described based on the deviation from normality during the first half of the movement. While some patients show a greater deviation, others are closer to the healthy control range. Yet, regardless of deviation for normality at movement onset, all show a large deviation upon grasp completion. This may be linked to the various techniques applied when pinching the zip handle, whereby the original deviation during the standardised position shows differences in a relaxed state. For the lid MDP curves three clusters can be identified: one group shows constant, non-variable deviation from normality, whereas the other two show either an increased or a decreased deviation from normality during the finger extension phase of the movement, equivalent to the first half of the movement phase. An increased deviation indicates greater impairment of extension, whereas a lower deviation during extension, with an increase toward the grasp completion indicates more impairment for the flexion movement.

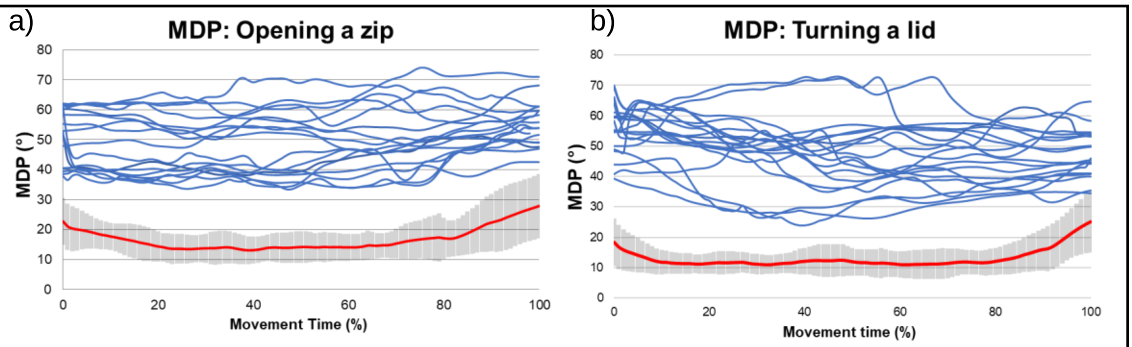

Figure 12: Movement Deviation Profile (MDP) curves for the zip (a) and lid (b) tasks, based on angles of all joints from onset of movement to task completion, showing that patient movements (blue, different shades equivalent to different patients) differ significantly throughout the entire movement phase from unimpaired healthy controls (red ± 1SD (grey)) in both functional tasks. The deviations show no clear pattern for all the participants of the patient cohort but clusters of patients for deviations can be identified.

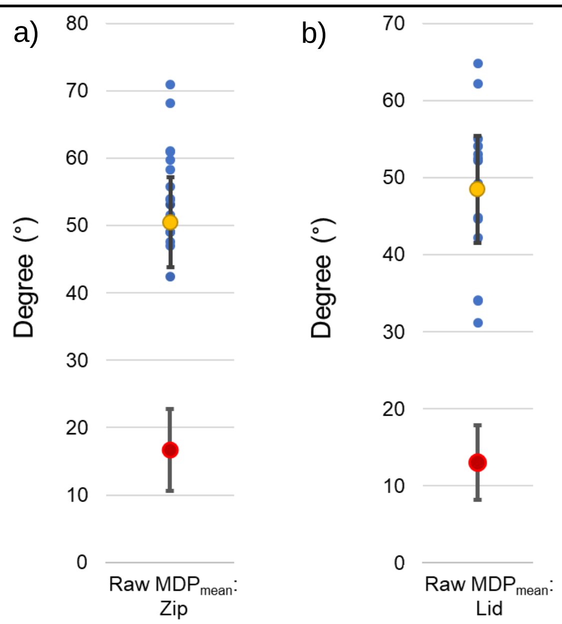

Figure 13: MDP_{mean} prior to z-score standardisation showed significant deviations of all patients (blue) when compared to the healthy control (red) (Healthy control mean ± 1 SD) for both the a) zip and b) the lid task. All patients showed significant deviations from normality (all $p < 0.05$) across both tasks. In yellow, patient mean ± 1 SD.

Eliminating specific joints from the MDP analysis did change deviations from normality for every joint. The standardised overall patient average of the MDP_{mean} was determined (Lid: 7.26 ± 1.80; Zip: 5.57 ± 1.55 (mean ± SD) (Figure 14 1a and 2a) and compared to the average MDP_{mean} after a joint was eliminated. The zip task, resulted for all joint eliminations in reductions of the MDP_{mean} greater than one standard deviation of the task specific overall MDP_{mean} (Figure 14 1b). For the lid task, all joint

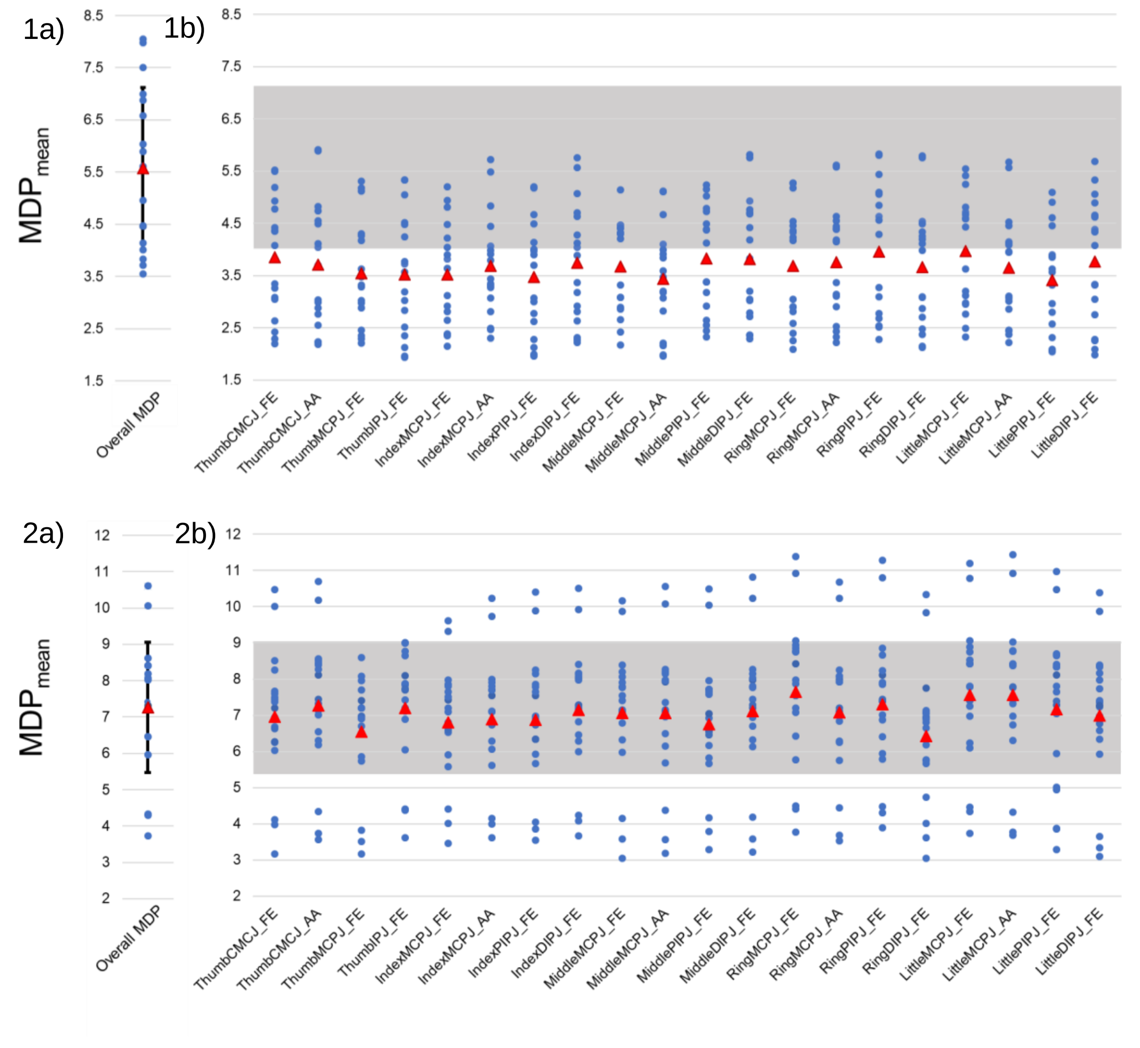

Figure 14: Movement deviations from normality were assessed for the whole hand (1a and 2a), as well as after the elimination of individual finger joints (1b and 2b) for two functional tasks: 1) opening a zip and 2) opening a lid. The data was standardised to the mean of the healthy controls using the z-score. In a systematic approach the angle curve of one joint was eliminated at a time (eliminated joint named on x-axis) to determine the impact of specific joints on the overall MDP_{mean}. Individual patient data (blue circles) is spread around the patient mean (red triangles). The standard deviation of the overall MDP_{mean} of patients was calculated (1a and 2a). In the lid task, all joint eliminations resulted in changes of the MDP_{mean} within 1 SD of the overall MDP mean (grey shaded area). In the lid task, all joint eliminations resulted in reductions of the overall MDP_{mean} that were greater than 1 SD of the over MDP_{mean}, therefore outside the grey shaded area.

eliminations resulted in changes of deviation from normality which were within one standard deviation of the overall MDP_{mean} (Figure 14 2b). Assessing the z-scores of the two tasks, it is apparent that the lid showed higher scores compared to the lid task, thus indicating patients struggled more with opening a lid compared to the zip. Further the patients showed reduced MDP_{mean} z-scores for the zip task after eliminating single joints, while the lid z-scores after joint elimination remained the same (within one standard deviation). As opening a zip involves flexion only, while opening a lid requires extension, it can be suggested that flexion range is less impaired than extension range across all joints. There was no pattern that clearly singled out a single joint or degree if freedom which was consistently impaired in all patients or showed greater contributions to the deviations from normality for either of the tasks addressed. Instead, it is suggested that movements are evenly impaired at all joints and movement deviations are highly variable among the patient cohort as shown by the wide spread of data around the patient mean.

4.4.3. Relationship of the MDP_{mean} to clinical measures of movement

When assessing individual correlations between the raw MDP_{mean} and clinical measures to identify a clinical measure that could indicate the MDP_{mean} in clinical practice, only one moderate, but significant interaction was identified for the lid task between the MDP_{mean} and movement time ($p = 0.01$, $R = 0.58$). Any combination of two clinical measures revealed moderate to strong correlations with the raw MDP_{mean} for the lid task, apart from the combination of disease duration and movement time ($p = 0.06$). No significant correlations between single clinical outcome measures and the zip task raw MDP_{mean} was identified and only the combination of FTP and MEA_{mean} was strongly predictive of the raw MDP_{mean} (Table 4). Weak to moderate correlations were identified between the MDP and individual clinical outcome measures (Figure 15 a-h) whereby the strength of association between the clinical variables and the raw MDP_{mean} was consistently stronger for the lid task compared to the zip task.

Table 4: Statistical analysis of regression tests to evaluate the strength of association between clinical outcome measures and the raw MDP_{mean}. The raw MDP_{mean} was correlated to the Finger-to-Palm index (FTP), years since diagnosis with SSc (Disease duration), time required to complete the task (movement time) and mean maximum extension angle (MEA). Multiple regression analysis was performed to evaluate the predictive strength of multiple clinical measures for raw MDP_{mean} outcome. Pearson's correlation coefficient (R) was determined and tested for significance (*p*) and the coefficient of determination was calculated (r^2).

	Zip			Lid		
	R	*p*	r^2	R	*p*	r^2
MDP + FTP	0.31	0.23	0.10	0.34	0.15	0.12
MDP + Disease duration	0.31	0.25	0.09	0.24	0.32	0.06
MDP + Mov Time	0.04	0.90	0.00	0.58	0.01 *	0.34
MDP + MEA	-0.05	0.84	0.00	0.30	0.21	0.09
MDP + FTP + MEA	0.74	0.02 *	0.54	0.72	0.01 *	0.52
MDP + FTP + Disease Duration	0.49	0.33	0.24	0.69	0.02 *	0.47
MDP + FTP + Movetime	0.34	0.67	0.12	0.69	0.02 *	0.48
MDP + MEA + Disease Duration	0.31	0.74	0.10	0.63	0.05 *	0.40
MDP + MEA + MoveTime	0.15	0.96	0.02	0.81	0.00 *	0.66
MDP + DiseaseDuration + MoveTime	0.41	0.52	0.17	0.62	0.06	0.39

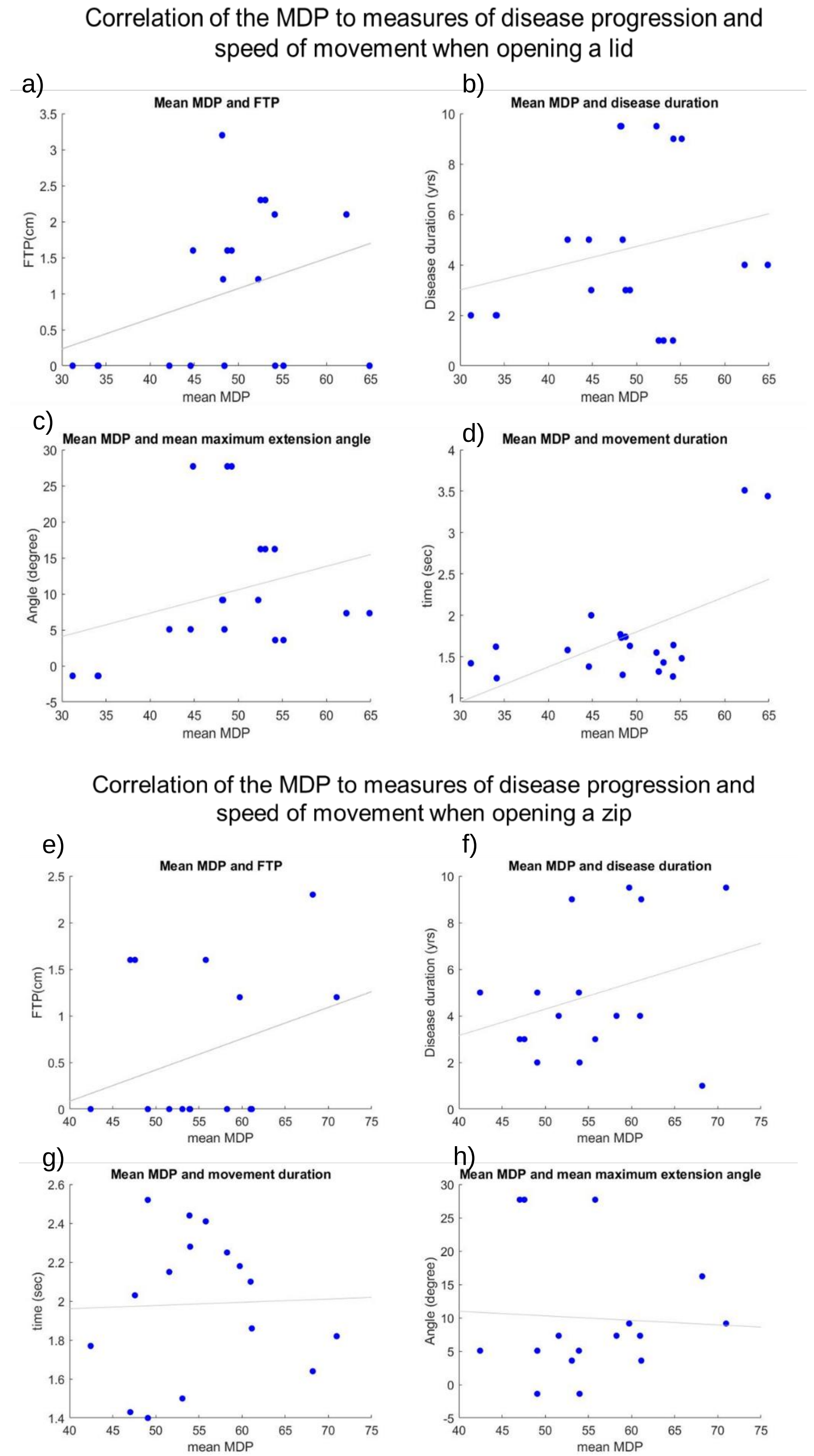

Figure 15: Correlations between the whole-hand overall raw MDP_{mean} and measures of movement (FTP and disease duration, movement duration, MEA_{mean}) were very weak to moderate for both tasks. Only the interaction between raw MDP_{mean} and movement time when opening a lid was significant ($p < 0.05$).

4.5. Discussion

A comparison of kinematic movement parameters between patients with SSc and a healthy age- and dominance-matched control cohort showed that patients present with significant movement deviations from normality throughout the entire movement phase. Movement is impaired for the whole hand and no individual joint could be identified to influence the MDP results significantly more or less than any other joint. Further, patients with SSc required significantly longer to complete the functional tasks assessed in this study.

The significant deviations of the patients from normality throughout the movement phase of both functional tasks supports the outcome of qualitative research of hand function in SSc (Erol et al., 2018; Sandqvist et al., 2004b). These deviations are not due to a joint specific limitation, but rather owing to a combination of joint adaptations in all fingers simultaneously, which could explain the overall significant increase of the MDP_{mean} in all patient participants for both tasks. The kinematic and kinetic chains of the hand mean no finger movement is truly independent (Mirakhorlo et al., 2017; Wilhelm et al., 2014). Therefore, motion impairment in one joint will trigger a change in movement profile in the neighbouring joints. Patients showed significantly impaired movement of all finger joints for both FE and AA movement. The clinical manifestation of SSc considers the interphalangeal joints to be predominantly affected by finger flexion contractures (Mouthon, 2013; Roberts-Thomson et al., 2006; Williams et al., 2018a), which contradicts our findings. The MCP and the TM joint are the most proximal mobile finger joints and movement limitations in these joints will therefore partially impair movement in the IP joints (Coupier et al., 2016) as well as the adjacent MCP joints. When assessing individual joints, no single joint showed significantly different effects on the MDP_{mean}, but rather an equal level of contribution of all joints to the movement impairment.

The single value MDP_{mean} provides a summary measure of the multi-joint deviation of movement from normality assessed in the single MDP curve. The FTP assumes intrinsic symmetry of hand impairment, meaning that all finger joints are equally affected. The findings of this study show that all finger joints are impaired evenly on average across multiple participants, which supports the reasoning of the FTP. This is further supported by moderate correlations between FTP and full hand MDP_{mean} of both functional tasks. While single clinical measures failed to predict the MDP_{mean}, the combination of multiple clinical measures showed significant interactions with the MDP_{mean}. In particular the combination of FTP and MEA_{mean} showed strong interactions with the MDP_{mean} for both tasks providing empirical evidence that movement limitations in SSc need to be assessed by considering multiple directions of movements rather than a single outcome measure. The MDP_{mean} could be used as a measure of cross-sectional movement deviations to evaluate the dynamic movement impairment, but also longitudinally as a measure of disease status and progression. Therefore, the MDP_{mean} could be the objective tool for overall hand function assessment in patients with SSc that is currently lacking in clinical practice. A 3D motion analysis, as essential for the MDP, is however cost and time intensive, thereby reducing the chances of the MDP being translated into clinical practice. A multidimensional analysis combining all clinical factors to predict the MDP_{mean}, without the use of motion analysis would therefore be ideal and should be evaluated in the future.

Patients were not able to extend their finger into a flat position, despite some being able to achieve a finger-to-palm distance (FTP) of zero, which would be interpreted as no impairment. This finding suggests that extension range is impaired prior to flexion and cannot be detected by the FTP test. Therefore, especially during early disease stages the extension of fingers (MEA_{mean}) provides valuable information regarding disease progression. Here the MEA_{mean} was acquired using motion analysis, which correlates well to the MDP_{mean} when combined with the FTP. Given the high cost of 3D motion analysis using reflective markers, in clinical practice the MEA could be assessed by a finger extension test, such as the positive prayer sign test. The positive prayer sign test is not validated in SSc, but has been used to measure hand movement impairment in Type I diabetes and cardiac conditions (Duffin et al., 1999; Kundra et al., 2017). To the author's knowledge, no other study has evaluated extension range of motion as a separate outcome measure in patients with SSc. Further, abduction-adduction is limited in the MCP joints of digits 2-5 and the TM joint. While not as critical as the FE range, the ability to spread out the fingers does contribute to ability to perform ADLs independently and without the need of specially adapted utensils (Cinar et al., 2014). In clinical practice AA ROM could be assessed using a finger spread test, measuring the distance between fingertips or side-to-side hand span during a maximum abduction in clinical practice. Simple methods to assess range of motion in all directions and fingers should then in future research be correlated to the MDP_{mean} in an attempt to overcome the cost barrier and generate a tool to translate simple outcome measures into clinically useful information.

Improving or at least maintaining mobility levels of the hand is the aim of both pharmaceutical and non-pharmaceutical interventions (Piga et al., 2014; Poole et al., 2013c; Rannou et al., 2016; Stefanantoni et al., 2016; Willems et al., 2015b; Williams et al., 2018a). Improved flexibility of the affected connective tissue should thereby lead to increased joint range of motion, and potentially reduced deviation from normality and irregularities in temporal movement curves and ultimately a reduced burden of disease during daily activities. Data presented in this study indicates that movement impairment are affecting all joints evenly, however, it is possible that more proximal joints exaggerate the measured impaired of more distal joints through the kinematic and kinetic chains. Multi-joint exercises training all joints within the patient's ability should therefore be preferred over single-joint or single finger exercises. Additionally, intervention programmes need to address not only flexion movements, but also train extension, abduction and adduction ability.

Only two functional tasks were evaluated in this study, the lid task requiring extension and abduction of all fingers into a spherical grip, while the zip task required a pulp pinch grip. There are six other functional grip types involved in the execution of ADLs. These are the diagonal and transverse volar grip, lateral, tripod and five-finger pinch as well as the extension grip (Sollerman and Ejeskar, 1995). Patients with SSc frequently report to struggle with any of the aforementioned grips (Cinar et al., 2012; Freire et al., 2013; Poole et al., 2013b) and these should be evaluated in future research. Further only the dominant hand was tested, despite some tasks often requiring the use of both hands.

4.6. Conclusion

Finger joint movement is significantly impaired in patients with SSc and each participant showed unique adaptations to the movement restrictions around the joints. Extension range is impaired prior to flexion in patients with SSc suggesting that rehabilitation programmes should focus on extension at the first instance rather than flexion. No single clinical outcome measure correlated to the MDP_{mean}, indicating that movement limitations cannot be quantified by a single outcome measure but require the multidimensional evaluation of various parameters. The combination of FTP and MEA_{mean} showed strong predictive strength for the MDP_{mean} in both functional tasks. Therefore, a simple test for finger extension ability, such as the positive prayer sign test, should be included in clinical practice in addition to the FTP. Abduction range impairments could be assessed using a finger spread test, further enhancing the understanding of multidimensional movement impairments in patients with SSc. This needs to be addressed in future research. This objective assessment can inform future rehabilitation programmes with the goal to reduce the magnitude of movement deviations from normality.

Chapter 5: Method chapter - Design of a virtual rehabilitation game for systemic sclerosis informed by three-dimensional movement analysis

Thesis structure				
Chapter	Title	Structural design	Addressed Aims	Linking to Chapters….
4	A comparison of hand movements during functional tasks in patients with systemic sclerosis and age- and hand dominance-matched healthy controls	Experimental study: Comparing hand movements of patients with SSc to age-matched healthy controls to quantify joint specific movement impairments	**Aim I:** Accurately assess the hand movement limitations of patients with SSc during functional tasks using three-dimensional motion analysis	5 and 7
5	Method chapter: Design of a virtual rehabilitation game for systemic sclerosis informed by three-dimensional movement analysis	Developmental study: Technical chapter with a detailed description of the design of a virtual rehabilitation tool for patients with SSc	**Aim III:** Deploy the portable motion capture method into a virtual rehabilitation context	7
7	Virtual Rehabilitation vs. Physiotherapy: A comparison of two rehabilitation approached on hand function in patients with systemic sclerosis	Experimental study: RCT comparing the effect of two intervention programmes to improve hand function in patients with SSc	**Aim IV:** Examine the effect of the virtual rehabilitation tool in comparison to traditional physiotherapy on hand movement limitations	3, 4, 5, 6

5.1. Preface

The objective assessment of hand movements in patients with SSc revealed impairments in flexion, extension, abduction and adduction ranges in all the applicable joints. There was no pattern to the degree of joint specific involvement contributing to the overall impairment. Chapter 2 outlined the impact of impairment on the patients' quality of life, and conventional approaches to reduce the disease burden at the hands. The conventional approaches do not target specific joints and mostly aim to improve finger flexion ability, which is insufficient based on data presented in Chapter 4. Further, conventional therapies are facing high drop-out rates, yet exercises are known to be most efficient when done regularly and long-term. A new intervention approach should therefore target all finger joints in all directions of movements and aim to overcome adherence barriers by increasing the patients' motivation and enjoyment during exercises.

The **aim** of this chapter was to create a novel virtual rehabilitation tool for patients with SSc, informed by the objective analysis of hand mobility conducted before. To achieve this, a game is designed in D-Flow, a software specifically for the design of virtual environments for rehabilitation purposes. The game will be driven by hand movements, which will be recorded by the Leap Motion controller. The Leap Motion generates a real-time data stream to the game, thus it will respond to hand movements which are specified in the game settings and informed by limitations as identified in the previous chapter (Chapter 4). The process is considered complete when the game is responsive to movement, and allows the adjustment of difficulty levels.

5.2. Background

Hand movement limitations in patients with SSc have been frequently reported over the past decades (Cinar et al., 2012; Poole et al., 2013b; Poole et al., 2013c) and are associated with increased anxiety and depression, and combined with reduced ability to perform ADLs and reduced quality of life. Further, in previous research (Chapter 4) a 3D motion analysis during functional tasks revealed that movement impairments are present in all joints and their respective movement directions (flexion, extension, abduction and adduction). Yet, traditional interventions focus on the FE range (NHS Inform, 2019; Scleroderma and Raynauds UK, 2016; Scleroderma Foundation, 2019; Willems et al., 2015a). A new rehabilitation approach should therefore target all joints, in all four directions of movement (flexion, extension, abduction and adduction).

Physical therapy was found to be an effective intervention to reduce hand involvement and increase the ability to perform ADLs short-term (Antonioli et al., 2009; Askew et al., 1983; Poole et al., 2013a; Rannou et al., 2017). Only 12% of patients who are referred to occupational or physical therapists actually start on a rehabilitation programme (Bassel et al., 2012) and most of these patients report a short adherence to the programme. Therefore an intervention method to improve adherence is desirable. Virtual rehabilitation was shown to be successful in the past for several conditions including cerebral palsy, stroke and Parkinson’s disease (Barton et al., 2013; Bryanton et al., 2006; dos Santos Mendes et al., 2012). Virtual rehabilitation uses computer games, which are played using body movement of a patient. Studies reported an increased motivation to follow the training programme owing to the playful environment. Virtual rehabilitation was considered more enjoyable and convenient compared to traditional approaches. Besides the playful environment, patients also value the immediate feedback of a bio-feedback computer game and the ability to learn about their movement impairments and improvements thereof immediately. Changes in performance are instantaneously visible making the training intervention more interesting and motivating (Bryanton et al., 2006). Virtual rehabilitation may therefore have some benefit over traditional physiotherapy for SSc by providing a potential solution to the adherence barrier. A suitable game for patients with SSc needs to be created and tested in comparison to conventional therapies to determine the suitability of VR for patients with SSc in real-life as such data is currently lacking in the literature. As physiotherapy exercises can be done at home without supervision, the VR tool should also fulfil this requirement.

The aim of this study was to create a portable, virtual rehabilitation tool for patients with SSc to train finger mobility in all permitted directions of movement. For the design of this tool the domains of the Template for Intervention Description and Replication (TIDieR) (Hoffmann et al., 2014) checklist should be considered. While the second domain, focussing on the reasoning for the intervention design, has been addressed in this introduction, the remaining, planning related aspects of the TIDieR checklist are addressed throughout this chapter, as well as Chapter 7 of this thesis, and highlighted appropriately.

5.3. Development

The customised computer game for this study was created in D-Flow 3.28.0 (Motekforce Link, Amsterdam, The Netherlands), a program forming part of the Computer Assisted Rehabilitation Environment (CAREN) system. The software allows design of virtual environments used for rehabilitation and training purposes. For this project the usually inactive Network module was enabled which allowed the link of the LM to the CAREN system, using a customised computer program (see Chapter 3) (TIDieR Domain 3: Materials required for the intervention).

5.3.1. Leap Motion

The LM can be used to measure hand movements by extracting joint centres from the integrated algorithm (for details see Chapter 3). The device is small and portable, and can be used on any computer or laptop by connecting via a USB cable. Therefore, the LM fulfilled the requirements to make this virtual rehabilitation program portable.

5.3.2. Game design overview

The design of this virtual rehabilitation tool was inspired by the game Flappy Bird, a huge gaming success in 2014. Flappy bird was a two-dimensional game, with the objective being to direct a flying bird between obstacles. The bird, which appeared to move towards the right, should not touch the obstacles that were moving past. If the obstacles were touched the player lost. To keep the bird flying, and preventing it from touching the obstacles, the player tapped the screen of a smartphone or the spacebar, if on a computer. Without tapping the bird fell to the ground due to gravity. The game speed, gap size between obstacles, fly/fall velocity of the bird were fixed, thus the game was unresponsive to the player's level of ability or progress (Igenito, 2014). A flappy bird replica was deemed a good option for a VR game for patients with SSc due to the simplicity of the task and ability to easily manipulate game parameters to create a difficulty-ability match between the game and the person playing.

The flappy bird replica in this study, from here on referred to as FlappyBall, was created to train finger mobility of all joints in their available degrees of freedom. A subjects' finger movement drove the game, which was achieved via a real-time data stream from the LM to D-Flow. The movement of all finger joints in 3D space was recorded, however, only a few data points were actually used to drive the game mode. The game could be played using two ranges of movement, which were shown to be impaired in patients with SSc (Chapter 4): Flexion-Extension range (FE) or Abduction-Adduction range (AA). The direction of movement was determined by a setting in the game prior to starting the game: If the parameter was set to 0, the FE range was used to play the game. If the parameter was set to 1, the AA range was determined and used to drive the game play.

A calibration and a game mode were designed. The calibration mode measured the range of motion of the subject in the specified direction (FE or AA). The measured ROM was then used to play the game in play mode. The next two sections highlight the exact processes of the game and the responsiveness to finger movements driving the game, which were previously identified as impaired. Given the separate modes both sections are relevant to the fourth domain of the TIDieR checklist as they describe the processes of the game that the participant would experience.

5.3.2.1. Calibration

The calibration mode was used to measure the ROM prior to playing the game. Three-dimensional data of 19 finger joints and five fingertips (72 data points per frame) were streamed from the LM to D-Flow through the custom-made C# program. The 3D position of the joints and tips relative to one-another allowed the calculation of the ROM during specific tasks at each joint as described below. The 3D position of the finger within the FE or AA ROM of the specific subject was used to drive the game.

While several ROMs could be calculated based on LM data, for this project simply the distance between two points was used. An indirect measure of the FE ROM was calculated as the difference between the maximum and minimum distance between the index fingertip and index CMCJ during a maximum voluntary flexion-extension task during calibration. The AA ROM was calculated as the difference between the index and middle fingertips during a maximum voluntary abduction and adduction task during calibration. Finger flexion is a multi-joint task and calculating the range as the difference between maximum flexion and extension angle of a single joint would not appropriately reflect the movement of the whole finger or hand. If a subject were to understand which joint was used to drive the game, they could simply move that particular joint (e.g. the TM joint), thereby reducing the potential effects of training on

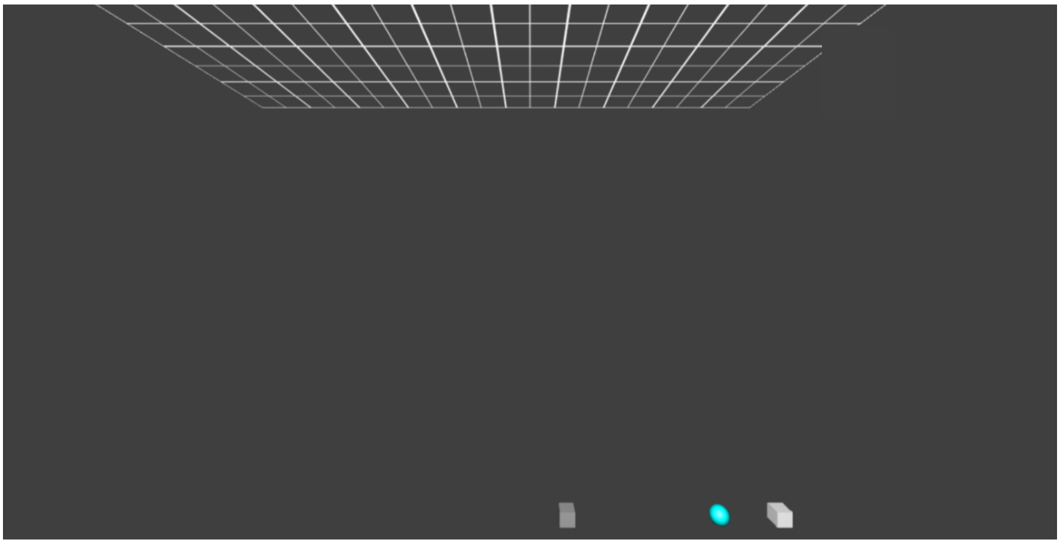

Figure 16: Calibration mode of FlappyBall. The boxes reflected position of the finger during maximum flexion or adduction (dark grey) and maximum extension or abduction (light grey). The blue ball indicated the position of the finger within the ROM.

the other adjacent finger joints. To determine the range as a mean angular displacement of several joints would be difficult in pathologic subjects, such as patients with SSc. If movement of several joints was impaired, the overall range of motion to drive the game was reduced, thereby diminishing the training effect of the game on slightly less impaired joints. By using the change in distance between two points, all finger joints had to be maximally used in the specified direction, which also prevented possible adaptive mechanisms to successfully play the game. For visualisation (Figure 16), a cyan coloured sphere was shown, representing the distance between two points (either the index fingertip and Index CMC joint or index fingertip and middle fingertip) in real-time. The maximum flexion or adduction position and maximum extension or abduction position were determined by attaching cube-shaped objects to the sphere representing the finger when the endpoints of movement were reached. This was achieved by generating buttons on the D-Flow console, which generated global events in D-Flow when clicked. One button, called ‘Snap to Max’, triggered an event which was used to attach an object to the 3D coordinates of the position of the sphere, thus finger position, at the time of activation. The ‘Snap to Max’ clicked by the operator of the game upon the participant reaching maximum extension or adduction. A second button, ‘Snap to Default’, was created, which was linked to a separate event to attach a second cube to the position of the finger at the time of activation. The ‘Snap to Default’ button was clicked upon maximal finger flexion or abduction depending on the range which was calibrated. Therefore the distance between the two cube-shaped objects was a relative representation of the ROM used to drive the game. The subjects could familiarise themselves with their range by moving the cyan coloured ball between the boxes. The position of the finger within the range was the determining factor of success in the game.

From the calibration mode two values were extracted into a text file: the ROM measure and the marker position when fully flexed or adducted. This text file was then used in the play mode to calculate the finger position within the range at a given time. Even though the FE and AA ranges were only calculated between two points, this was not relayed to the subject playing the game. During the calibration mode, the subject was instructed to flex all fingers maximally, followed by a maximal extension of all fingers simultaneously. Similarly, during the AA calibration the subjects were instructed to squeeze all fingers together, followed by a maximum abduction of all fingers simultaneously. Hence the subject had no knowledge of the actual computation of the ROM used for the game play.

5.3.2.2. Game mode

Five obstacles were created for this game. Each obstacle involved a lower and upper element with a vertical gap in between. The combined height of each obstacle was ten metres. The gap height was adjustable, to increase or decrease difficulty. The maximum gap height, thus easiest setting, was nine metres, leaving only one metre of obstacle at the top or bottom. The smallest gap height was one metre. The location of the vertical gap was randomised. At the start of the obstacle a new number was generated by a randomiser, shifting the vertical gap location upwards or downwards

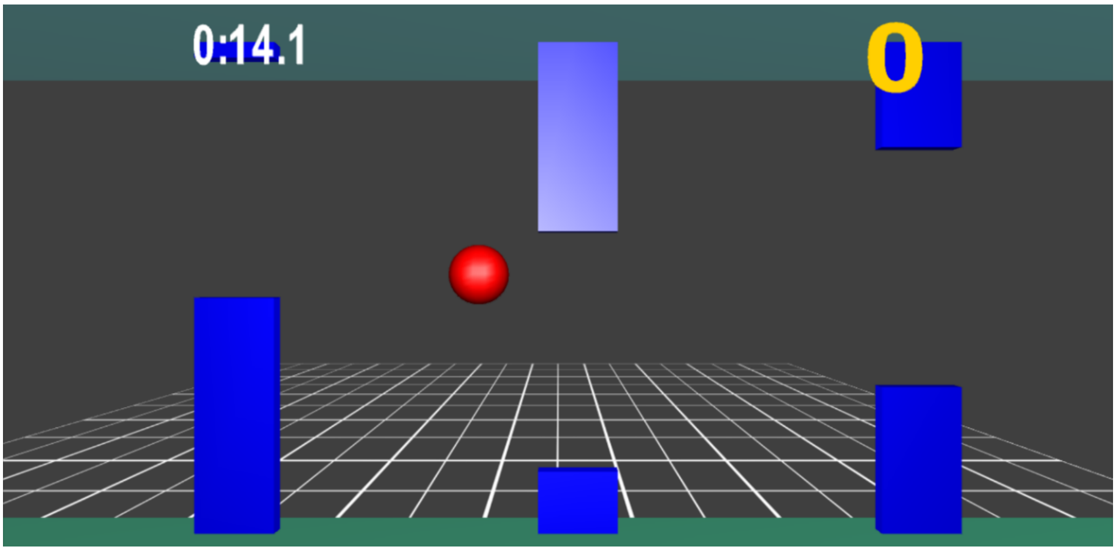

Figure 17: Game mode appearance of FlappyBall with default settings. The red ball was directed through an obstacle course by moving the finger through the ROM. The ball jumped once the finger entered the last 20% of the ROM. An error score was displayed (yellow number, top right corner). This number increased in single step increments if an obstacle was touched. Time is presented in the top left corner.

relative to the previous gap location. The random number reflected the vertical scaling factor of the bottom part of the barrier. Taking into consideration the pre-defined gap height and lower element scaling factor, the vertical scaling of the upper element can be calculated to not exceed 10 m. Consequently both vertical gap location and upper element vertical scaling depended on the vertical scaling factor of the lower elements determined by the randomiser. The horizontal distances between the obstacles was defined by a second game parameter, called gap size. The gap size between the obstacles was defined as 4.67 m, which reflects the horizontal distance between objects at which the gap size between the looped obstacles is always constant (Figure 17). The obstacles moved from right to left. The movement and order to these obstacles was programmed using mathematical equations, based on time, horizontal gap size and game speed. The position of each obstacle was calculated by multiplying time with game speed (manually adjusted parameter, between 0.1 and 10) and subtracting the product of gap size times obstacles number, whereby the first obstacle was 0 and the last one 4. As time changed continuously, the obstacle moved across the screen from right to left. Gap size was multiplied by obstacle number, therefore the obstacles appeared in the same distance relative to each other. The five obstacles were looped. If the position formula exceeded -11 on the x-axis (outside of the visual field of the game mode), the obstacle was reinitiated at the original position (+11 on the x-axis, outside of the visual field of the game mode).

A ball (Ø 0.75 m) was created, which needed to be directed through the obstacle course during game play. The ball movement was limited to the vertical axis, and the starting position was set to 6 m vertical distance to the bottom. During game play, the ball position was defined in a script using multiple input sources. The position of the finger within the ROM, as determined during the calibration trial, was calculated as a ratio, whereby 0 indicated the finger was maximally flexed/adducted and 1 indicated maximum extension/abduction. The position of the finger within the range was linked to the movement of the ball. Instead of tapping a screen or spacebar, in FlappyBall a jump of the ball was achieved by moving the fingers towards the maximum extension (for FE range) or maximum abduction (for AA range) position. A single upward acceleration of the ball, or bounce, was achieved by moving the finger into the last 20% or the extension range (FE range) thus exceeding the ratio value of 0.8 (AA range: last 10%, exceed ratio 0.9). When the threshold was exceeded, the velocity of the ball was made equal to the jump speed, hence the ball direction would change and result in an upwards motion of the ball.

Two additional parameters affected the falling and jumping of the ball: the gravity multiplier and jump speed. The script (Appendix 1) defined gravity as 9.81 $m.s^{-2}$ (gravitational constant) multiplied by the manually adjustable value of the gravity multiplier. Gravity was acting on the ball, which at start of the game, was thought to have no velocity at the beginning of the game (v = 0). The ball was further offset vertically by four units (s = 4). For every frame velocity (v) and position (s) of the sphere were re-calculated relative to the previous frame. Therefore, the ball would fall to the ground in the absence of sufficient finger movement. Manipulating the gravity multiplier would increase or reduce the rate of falling, thereby allowing adjustment of game

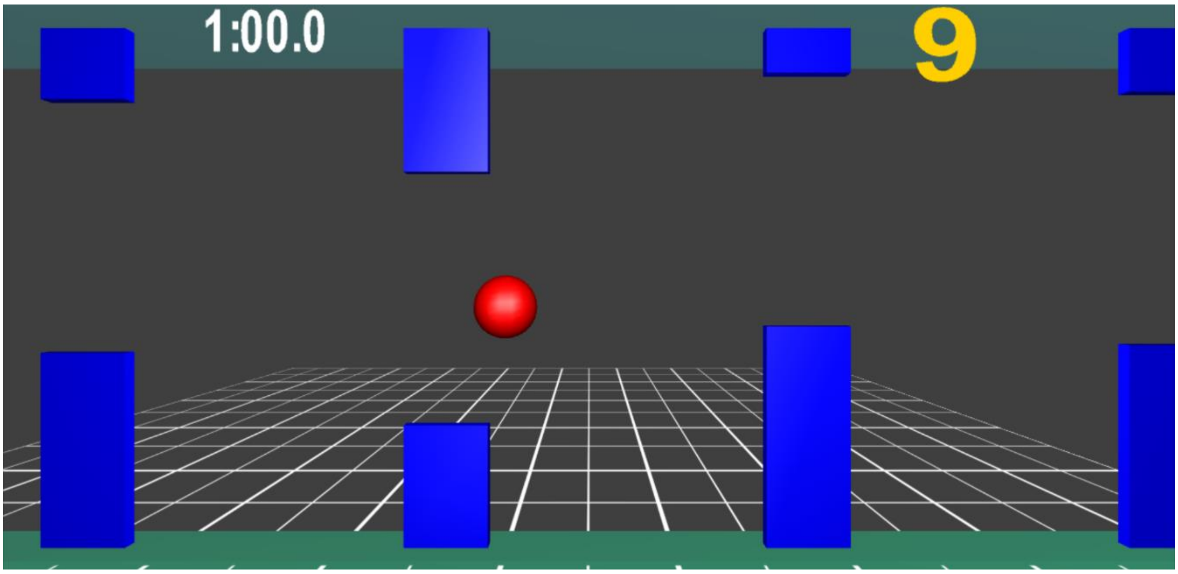

Figure 18: FlappyBall play mode stopped automatically after one minute (timer in top left corner). The ball stopped moving and the final number of errors made in one minute (top right corner) was saved.

difficulty to the player's ability. The jump speed, which determined the upward velocity of the ball in the presence of sufficient finger movement, was also adjustable. The higher the jump speed value, the longer the upward jump of the ball lasted, thus reducing the difficulty of the game.

The task of the game was to direct a ball through the gaps in obstacles without touching said obstacles. In the original Flappy Bird game, the touching of pipes by the bird would result in the 'death' of the bird and one had to start over. In this game, the collision between ball and obstacle did not stop the game. Instead, an error point was awarded. The error points were accumulated until the end of a trial, and provided feedback to the player. A lower score thereby reflected a greater success rate at the game. The game was played for one minute (Figure 18). After one minute the game automatically stopped and reset itself ready for the next trial. At this stage, a one minute limit per set included approximately 29 repetitions at default settings. The intensity (number of sets and sessions per week) of an intervention needs to be tailored to a specific disease (Domain 8 of the TIDieR checklist).

At the end of each trial a text file was generated, containing the ROM, absolute maximum and minimum distance between the defined two points of the hand, game parameter settings used to play the game, repetitions made (counted as number of times the threshold to initiate a jump was crossed) and the error score.

5.3.2.3. Difficulty settings and individualisation

In addition to mapping the individual's available range of motion, three key parameters could be manually adjusted in the console (Figure 19) to increase or decrease the difficulty of the game to match the ability of the subjects, which also addressed the tailoring domain of the TIDieR checklist (Domain 9). Matching ability and difficulty of games is deemed important to ensure the player can have fun exercising rather than getting frustrated because the game is too difficult, or bored because the game is not challenging their skills. Initially each participant started with the default settings. These were determined by qualitative, verbal feedback of healthy volunteers commenting on the perceived difficulty of the game (Appendix 8).

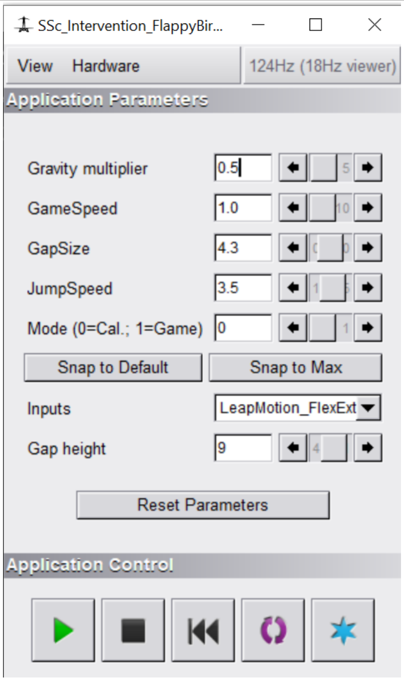

Figure 19: FlappyBall game settings could be adjusted manually. The rate of falling of the ball was regulated by the 'Gravity multiplier', the rate of the ball jumping by 'JumpSpeed', horizontal gap size between obstacles by 'GapSize', and vertical gap size within an obstacle by 'Gap height'. The switch between calibration and play mode was determined by 'Mode'. The 'Snap to default' was activated upon maximum flexion or adduction, and the 'Snap to Max' was applied upon maximum extension or abduction. The movement used to drive the game was determined in 'Inputs'.

The gap height was the primary parameter used to adjust game difficulty. The reduction in gap size required the subject to improve the timing of the finger crossing the threshold. A crossing of the threshold too early or too late would result in a collision with an obstacle. The default setting was 8 m. In this condition, the obstacles are very short, allowing the subjects to familiarise themselves with the movement that drives the game as well as the game itself. The gap height was adjusted in 1 m increments. The gravity multiplier and the jump speed were adjusted to make the ball fall faster and bounce less, respectively. If the ball fell faster or jumped less the subjects had to move their fingers faster through the range that drove the game to prevent the ball from falling to the ground or touch obstacles. Changes in these parameters would also increase the overall number of repetitions made during one minute of game play. The jump speed was adjusted prior to the gravity multiplier. Both parameters were adjusted in 0.1 increments.

A single increment change in one parameter was followed by an adjustment in another parameter. Effectively, if the gap height was changed by 1 m, the next adjustment could not be a further decrease/increase in gap height. Instead the next adjustment had to be for jump speed, then gravity multiplier. This pattern also helped to address and record modifications when applying this game in an intervention study and thus addressed the modification domain of the TiDieR checklist (Domain 10).

5.4. Evaluation and application to the research studies

A game was created to train multi-joint finger mobility in FE and AA range. The game includes a calibration mode, which measures an individual's range of motion in either the FE or AA range, and the game play mode to train finger mobility. The calibration mode also allows the familiarisation to the ROM and movement required to play the game. Once switched into game play mode the ball was directed through the obstacle course by moving all fingers at the same time through the calibrated range (FE or AA), thus making this game a tool for multi-joint exercises. In play mode the game stopped after one minute to allow a short break between repeated games for the person playing. The game difficulty can be adjusted to match the player's ability level. FE range was targeted in most conventional therapies reported the in the literature, while AA range was rarely addressed in hand exercises for SSc patients. Most range of motion exercises address FE range in a single passive or active stretch, while holding the position for a specified period of time. Only Wolff et al. (2014) and Piga et al. (2014) included one exercise specifically for finger abduction in their training programmes. FlappyBall provides the option to dynamically train both finger flexion-extension and abduction-adduction movements, making this VR tool unique in the rehabilitation of hand movements in SSc. As FlappyBall targets all joints of the hand simultaneously in a dynamic task requiring the full active range of motion, the time demand for the FlappyBall exercise is low compared to the typically advised hand stretches and additional manual therapies. This could positively influence adherence to exercises as

Figure 20: FlappyBall was played on a Laptop using the LM as input device for hand movements. The system was portable and could be deployed in many locations.

the competition of training with other responsibilities is diminished. The game uses motion data measured with the Leap Motion controller as input source (Figure 20), making the created VR game portable and useable at the patient's home, although at this stage, the VR tool can only be used partly-supervised for initial studies examining the effectiveness of VR on hand movement limitations in SSc and motivation to complete VR based exercises. Once proof-of-concept is delivered this tool can be enhanced further, for example by playing the game with both hands at a time or in a multi-player setting to enhance competitiveness and increase motivation. For use in non-supervised, remotely monitored research, the game needs a simplified start-up, including a more automated calibration of the ROM, possibly using threshold calculations. Secondly, the adjustment of parameters to match difficulty to the patient's ability level would need to be either simplified, or best automatically adjusted based on the performance of a participant in the previous trial or over time within a trial. Automatic storage of training data to a cloud-based system, which can be accessed remotely by researchers or healthcare professionals could be implemented for data collection purposes and to evaluate progress over time, which can be addressed during routine clinical appointments.

5.5. Summary

A virtual rehabilitation tool to train finger extension, flexion, abduction and adduction in a multi-joint approach was created. The game uses interactive bio-feedback to train the active range of motion across all joints and fingers. The movements which drive the game were identified to be impaired in patients with SSc. Therefore, this virtual rehabilitation tool can be used to actively train the identified movement limitations, aiming to reduce the extent of the deviations from normality which were identified in a previous study (see Chapter 4). The tool is ready to support pilot studies on the effect or virtual rehabilitation on finger movement limitations in SSc.

Chapter 6: Improving the accuracy of the Leap Motion controller for purposes of markerless hand motion capture using artificial neural networks

Thesis structure				
Chapter	Title	Structural design	Addressed Aims	Linking to Chapters….
3	Describing the development of an opto-electronic and a markerless motion capture approach for the hand and subsequent kinematic modelling	Developmental study: Technical chapter outlining the design of kinematic models used in this thesis		4, 6 and 7
5	Method chapter: Design of a virtual rehabilitation game for systemic sclerosis informed by three-dimensional movement analysis	Developmental study: Technical chapter with a detailed description of the design of a virtual rehabilitation tool for patients with SSc	**Aim III:** Deploy the portable motion capture method into a virtual rehabilitation context	7
6	Improving the accuracy of the Leap Motion controller for purposes of markerless hand motion capture using artificial neural networks	Experimental study: Assessment of the Leap Motion controller to accurately measure hand kinematics before and after the application of neural networks in comparison to an opto-electronic measurement approach.	**Aim II:** Develop a portable method to capture 3D movement	7
7	Virtual Rehabilitation vs. Physiotherapy: A comparison of two rehabilitation approached on hand function in patients with systemic sclerosis	Experimental study: RCT comparing the effect of two intervention programmes to improve hand function in patients with SSc	**Aim IV:** Examine the effect of the virtual rehabilitation tool in comparison to traditional physiotherapy on hand movement limitations	3, 4, 5, 6

6.1. Preface

Chapters 2 and 3 reflected on differences in kinematic parameters if using different types of models or motion analysis approaches. In Chapter 3 two approaches to hand motion analysis and their kinematic models have been described, which have been/will be applied to quantify movement in patients (Chapter 4 and Chapter 7 respectively). However, the agreement between these two methods is not good. While a game (Chapter 5) does not rely on accurate kinematics and can be played with unmanipulated Leap Motion data, a motion analysis to determine effectiveness of a game later on (Chapter 7) does require accurate data. A marker-based opto-electronic approach is thought to be more suitable for research than the portable Leap Motion controller, due to higher accuracy. Yet the Leap Motion has the benefits to be portable and affordable. An ideal solution would therefore be a compromise of the two systems, taking the benefits of the two systems and combine them into a new approach to motion capture. This outcome could be achieved by improving the data accuracy of the Leap Motion controller. Artificial neural networks (NN), a form of artificial intelligence, have the ability to learn multi-dimensional relationships between low-quality data (such as the LM data) and high-quality data (such as from the Vicon system) during a training phase. Following successful training, the NN can then generate predictions of Vicon data in the presence of new low-quality data, effectively transforming the low-quality data from the cheap and portable LM into high quality, Vicon equivalent data.

The **aim** of this chapter was to evaluate the use of an artificial neural network (a form of artificial intelligence) to improve the accuracy of the Leap Motion when compared to a gold-standard opto-electronic motion capture system. To achieve this, movement was captured simultaneously with the Leap Motion controller and Vicon system and used to train and test an artificial neural network. Joint kinematics were determined for all three devices and the difference of the neural network output and Leap Motion data relative to the Vicon kinematics was analysed and tested for significance. The hypothesis is that the neural network approach significantly reduces the error of the Leap Motion.

6.2. Introduction

Opto-electronic marker-based motion capture is considered to be the gold-standard approach for movement analysis. The methods and systems have been validated multiple times using bone pin methods or MRI imaging (Benoit et al., 2006; Dzialo et al., 2018; Reinschmidt et al., 1997; Sandau et al., 2015), but marker-based motion capture has several limitations. The soft tissue artefact causes slight vibrations in surface mounted markers, leading to inaccurate motion capture results, especially around the joints or in the presence of adipose tissue. The systems required for tracking and analysis of skin-mounted markers are further expensive and expertise is required to use these systems. Last, motion capture using cameras are often rather stationary and lab-based, prohibiting the ability to make scientifically rigid assumptions about the translation from lab-based environment to real-world applications. In recent years the interest in markerless, portable devices has increased, to allow research in the field without the restrictions of markers or lab spaces (Simon, 2004).

The Leap Motion controller (LeapMotion Inc.) (LM) was designed for touchless interaction with computers. Using gesture recognition, the device can be recruited to perform any task on your computer or laptop. For this purpose the LM has two wide-angle cameras and three infra-red LEDs, to enhance hand recognition (Colgan, 2014). When holding a hand above the sensor, the device registers the position of the fingertips and palm relative to the device, and then reconstructs the hand skeleton in real-time in 3D (Colgan, 2014). Very little is known about the nature of the integrated algorithm. It is public knowledge that the skeleton is generated based on mathematical assumptions and the position of the centre of the palm and the fingertips relative to the device as recognised on video images (Colgan, 2014). The measurement of fingertip and palm position relative to the device is highly accurate under both static and dynamic conditions (Smeragliuolo et al., 2016; Weichert et al., 2013). The ability to accurately identify hand position is essential for the gesture recognition it was originally designed for. Yet, due to the calculation of joint centre locations in 3D space, the LM has greater potential for motion analysis of the hand. Nizamis et al. (2018) compared hand and wrist angles measured with the LM and a goniometer and found poor agreements between the methods showing that the LM is inaccurate to measure the exact ROM. However, this study only evaluated the ROM not the temporal-spatial accuracy throughout dynamic movements, which is typically assessed using opto-electronic motion capture. In a pilot study with a single subject (Appendix 7) an error of up to 36° RMSE for the flexion-extension angles of an index finger joints was identified supporting the findings of Nizamis et al. (2018).

Artificial Neural Networks (NN) are mathematical models, inspired by the structure of the biological brain. In the presence of input data and target data, a layer of neurons integral to the NN learns the non-linear, multi-dimensional relationship between two data sets and generates an equation that reflects this relationship. This process is called the training phase. The success of training to develop a sturdy and precise NN is linked to the quality and quantity of data inputs. Following successful training, a NN generates an accurate prediction of theoretical target data when provides with previously unseen input data. In theory, a trained artificial neural network should be able to accurately predict high quality motion data from low-quality input data, such as from the Leap Motion, thereby turning the LM into a cheap, portable and easy to use system for motion analysis. In recent years, NNs have been applied in motion analysis, and several research groups have very recently applied deep-learning artificial neural networks to test markerless motion capture approaches of the lower extremity (Eliason et al., 2019; Kanko et al., 2019). The design of an accurate, portable and cheap motion capture device will enable researchers to conduct field testing outside of the laboratory, and for this thesis, to conduct an entirely home-based intervention study with patients including pre- and post-intervention assessments of hand mobility.

The aim was to improve the accuracy of the Leap Motion using artificial neural networks and the marker-based motion capture data as gold-standard target data, as previous research suggests LM inaccuracies for assessing dynamic movement and range of motion.

6.3. Methods

This study was conducted in two parts, whereby the second part was informed by the outcome of part one. The first part was to improve the accuracy of the LM during random hand movements using artificial neural networks. Artificial neural networks require substantial data input and multiple data points for all types of movement. Therefore, in the second stage we then aimed to generate task specific neural networks, which reflect the movement of fingers through the ROM in specific directions. This study was approved by the University Research Ethics Committee (17SPS/027).

6.3.1. Participants

For both parts of the study 15 young healthy adults were recruited. All participants had no history of surgery or illnesses of the hand, and were injury free for at least six months. All subjects provided written consent to participate in this study.

6.3.2. Data collection

LM and 3D motion capture data were captured synchronously. Participants were fitted with a 48 marker setup on the dorsum of the hand (see Chapter 2). The markers were tracked using 15 MX (eight T160 and seven T10) Vicon cameras (Vicon Inc., Oxford, UK), mounted on a customised 1.5 m x 1.5 m x 1.5 m cube-shaped frame. The volume was calibrated using a custom-made calibration tool, and the origin was set at the centre of the cube. The LM was placed at 40 cm height above the ground slightly below the centre of the camera volume.

Once fitted with the markers, subjects were seated on a height adjustable stool. The subjects were positioned to hold their hand in the centre of the camera volume, with a shoulder flexion angle of 45° and 20-25 cm vertical distance to the LM. The wrist was supported during this data collection to maintain the same position relative to the device. The literature identified this distance between hand and sensor to be most accurate (Weichert et al., 2013).

The marker data was tracked in Vicon Nexus 2.5 (Vicon Motion Systems Ltd., Oxford UK) and transferred to D-Flow (Motekforce Link, Amsterdam, The Netherlands) via the local PC network and Markermatcher module. Joint coordinates from the LM were streamed across to D-Flow via the Network module and the C# program (see Chapter 2 for details). As both methods recorded the movements simultaneously, and in real-time, the devices were synchronised for sampling. The 3D coordinates of markers and joint centres were recorded at 300 Hz in tab-separated text files by two Record modules.

In the first part, all participants performed 15 x 20 seconds of self-selected hand movements with their left hand only. Participants were instructed to only move the fingers, maintain a parallel position of the palm relative to the LM and not move the wrist or shoulder. The direction, range and speed of finger movements were chosen by the participant. After each trial the subjects were given a short recovery period, to relax their shoulder, elbow and wrist.

In the second part of this study, all participants performed 5 x 15 seconds of structured hand movements of three tasks with both the left and right hand separately. The tasks were:

1) Flexion-extension movements: Participants were moving their fingers from maximum, active extension, until ~75% of maximum flexion. The thumb was also included, and participants were instructed to place the thumb next to the index finger during flexion, instead of moving it diagonally across the palm. The palm was parallel to the LM. The flexion range was limited due to the technical limitations of the motion capture system.
2) Abduction-Adduction movements: Participants were instructed to hold their hand flat and parallel to the LM. The participants were instructed to maximally abduct the fingers, followed by an adduction movement with the fingers just loosely touching. The thumb was not included in this part, as participants found simultaneous abduction movements of the TM joint and MCPJ joints of digits 2-5 challenging and thumb AA range was included in the third movement.
3) Thumb circumduction: As in previous tasks, the hand was held parallel to the LM with all fingers in a flat position. In this task, only the thumb was mobile and digits 2-5 were held in a static position. Participants were instructed to draw a circle in the air with the thumb tip.

6.3.3. Data processing

Motion data acquired with the LM and Vicon systems was processed separately before analysis.

6.3.3.1. Marker based data

The Vicon marker data text file was formatted, imported into Visual3D (C-Motion, Germantown, WA, USA) and from there exported as c3D file. The c3D file was then loaded into Vicon Nexus 2.5 (Vicon Motion Systems Ltd., Oxford UK) for labelling and gap filling. The correctly labelled and gap filled file was then re-imported into Visual3D for modelling. A marker-based motion capture model was applied for this data set, including the calculation of functional joint centres from a static and a functional trial (see Chapter 2 for details). Following kinematic modelling and applying a 6Hz low-pass filter of the fourth order the three-dimensional coordinates of the calculated joint centres, fingertip and the three markers on the palm data were exported. All files were saved according to the initial subject and trial number from the original recording with the extension _JCTP (Joint centre, Tip, Palm) to be linked to the LM data recorded simultaneously.

6.3.3.2. LM data

Joint centre data was formatted for import into Visual3D (C-Motion Inc, Germantown, MD, USA). The movement of each trial was carefully analysed for glitches, which can irregularly occur with the LM and are linked to light reflections from the video background. If problems were identified the according frames were removed from both the LM and the corresponding Vicon text file prior to neural network analysis in Matlab. The LM algorithm applied an integrated filter to smoothen the data (Colgan, 2014), therefore no further filtering was applied on the LM data. The details of the filter applied to the LM raw data within the scope of the LM algorithm are unknown. All files were saved according to the initial subject and trial number from the initial recording with the extension _LM (Leap Motion). Therefore, all data could be linked to simultaneously recorded marker-based data.

6.3.4. Neural network analysis

The LM joint centre files and Vicon joint centre files were loaded into Matlab (MathWorks, Natick, MA, USA) into 3D matrices. The first dimension reflected frame numbers, the second dimension was linked to the 3D coordinates of joint centres, and the third dimension reflected individual trials. The LM and corresponding Vicon trials were loaded into their respective matrices in the same sequence.

The LM sampled at a variable rate of 30-60 Hz, thus at a lower rate than the Vicon system (120 Hz) and D-Flow (300 Hz). Therefore, the LM data changed only around every five to ten frames, yet the Vicon data would change every third frame recorded in D-Flow. The neural network learns relationships between data points, and therefore the same value recorded with the LM would correspond to three different data values acquired with the Vicon system, which would reduce the ability of the NN to accurately predict Vicon data. Therefore, the data was re-sampled to the lowest common frequency, i.e. the frequency of the LM. This was achieved by identifying the frames with a change in value relative to the prior frame in the LM matrix. Frames where no change relative to the prior one was identified were then removed from both the LM and the Vicon matrices.

LM and Vicon operate on different Cartesian coordinate systems. To bring the hands closer together and offset any differences in hand position within the capturing volumes, the hand position was standardised for the TM joint of both hands to be located in the origin throughout the movement phase.

Following the translation of the hands so that the TM joints were in the origin the 3D matrices were merged into 2D matrices by appending the trails below one another to create one matrix for the training of the neural network. Prior to training of the neutral network, a z-score was performed to standardise the data points to the mean of the whole data set. This was done to reduce the effect of hand and segment sizes. The z-score was followed by a principles component analysis (PCA) for dimension reduction. The original data sets had 69 (Vicon) and 72 (LM) dimensions, which is difficult for the NN to process, depending on computing power even impossible. The PCA also calculates a percentage of the total variance explained by each principal component (PC) within the data set. Based on this, a new matrix for LM and Vicon data was created: these matrices included the PC scores of the first *n* components, whereby *n* was determined to be the number of principle components explaining 95% of the variance in the original data set. The new matrices were then used to train the artificial neural network.

6.3.4.1. Neural network configuration

A shallow neural network for pattern recognition was configured in MatlabR2018a using the Neural Network toolbox (Version 11.1). As inputs to the neural network (NN) the LM PC score matrix was used, and the Vicon PC matrix as target data. The number of hidden nodes in the single hidden layer was determined as the average between input and target nodes to avoid overfitting or underperformance. The weights and biases of the neurons in the hidden layer, which can influence the NNs ability to predict data, are initialised using the random number generator (RNG), which generates a different random number every time the neural network is created. To control the weights and biases of the NN neurons, the RNG was controlled. At creation of any NN a random number is chosen by the computer, which sets the weights and biases of the neurons in the hidden layer. Further, if not controlled, the weights and biases change for every network initialised, thus reducing the replicability of the work. For this study the RNG was controlled using the value 19, which showed the best result when testing the effect of the RNG on the neural network (NN) output over a range from 1-1000. Although the effect of the RNG on NN output was negligible (range: 0.0035; Appendix 2).

The data sets were split up into 80% training, 10% validation and 10% test data, prior to training of the NN. A 10-fold validation was applied to circle through the data set to use each data point once for testing and validation (Seiff, 2019). K-fold cross-validation is a commonly applied statistical method in machine learning to estimate the power of a model and make an informed decision for a model based on predictive strength and reduced biases. Effectively the full data set is split into three sections (training, validation and test) in the first instance, such as 0-80% for training, 80-90% for validation and the last 10% of the data for testing. In the subsequent 10-fold validation the same original data set is split up again into training, validation and test sets, but every time a new data block is used for testing and validation of the NN (Figure 19). Subsequently 10 NNs were trained, validated and tested.

Following successful training the test data output, input and target data were reconstructed. In an initial step the PCA was reversed, by multiplying the test data with the PC coefficient and adding the mean. For the input data the LM PC coefficient and mean was used, whereas the output and target data was reversed using the Vicon PC coefficient and mean. Following successful reversal of the PCA all test matrices of input, output and target were merged into three accumulated matrices (T_Output, T_Input and T_Target). On the accumulated matrices the z-score was reversed. The accumulated matrix was essential as the reversal of the z-score can only be done on matrices of the same dimensions as the original matrix. Following reversal of the z-score, the T_ matrices were split up again into the 10 original test matrices to allow a performance analysis of every NN from the 10-fold validation separately. The reconstructed data is representative of the LM joint centre data (T_Input 1-10), measured Vicon joint centre data (T_Target 1-10) and NN prediction of joint centre data (T_Output 1-10). The data was exported for further processing and analysis in Visual3D.

6.3.5. Output analysis

The reconstructed data was imported into Visual3D where joint angles were calculated and exported for analysis. The joint angles included in the analysis were sagittal plane angles (flexion-extension) of nine IP, five MCP and the TM joint and frontal plane angles (abduction-adduction) of the digits 2-5 MCP and the TM joint (Table 4). The RMSE between the T_Input and T_Target, as well as T_Output and T_Target was calculated for each NN. The change in RMSE before and after applying the NN was calculated in percent to estimate the error reduction due to the NN correction. A

Table 5: 20 joint angles were analysed to assess the effectiveness of the NN to predict the target data. 15 flexion extension (FE) angles from all five finger (1-15) and five abduction-adduction (AA) angles (16-20) were examined.

Angle number	Joint	Direction	Angle number	Joint	Direction
1	TM	FE	11	Ring PIP	FE
2	Thumb	FE	12	Ring DIP	FE
3	Thumb IP	FE	13	Little MCP	FE
4	Index MCP	FE	14	Little PIP	FE
5	Index PIP	FE	15	Little DIP	FE
6	Index DIP	FE	16	TM	AA
7	Middle MCP	FE	17	Index MCP	AA
8	Middle PIP	FE	18	Middle MCP	AA
9	Middle DIP	FE	19	Ring MCP	AA
10	Ring MCP	FE	20	Little MCP	AA

correlation analysis between T_Target to T_Input and T_Output to T_Target was conducted to test if a linear relationship between the magnitude of angles as calculated based on the three methods was present. A strong correlation should therefore indicate substantial agreement of the angular profile over time. The correlation was tested for significance and the correlation coefficient (R), indicating the strength of relationship. The resulting p-values and R values were mapped using a colourmap. Additionally, the angles were plotted to visually compare the angles calculated for T_Input, T_Output and T_Target curves. All mathematical and statistical analysis was conducted in MatlabR2018a (MathWorks, Natick, MA, USA). The respective test results for T_Input and T_Output to T_Target were compared to quantify if the neural network could improve the kinematic profiling generated by the LM originally. The steps described above were repeated for all seven data sets (1. Random hand movements left hand, 2. Flexion-Extension left hand, 3. Flexion-Extension right hand, 4. Abduction-Adduction left hand, 5. Abduction-Adduction right hand, 6. Thumb circumduction left hand, 7. Thumb circumduction right hand). In the following results section only figures of the first attempt (random hand movements) are shown. All figures of the second to seventh data set are in Appendices 3-5 of this thesis. For all movements, 20 angles (Table 4) were assessed as these cover all movement degrees of freedom of the hand. All charts evaluate angles in the order outlined in Table 4.

6.3.6. Workflow summary

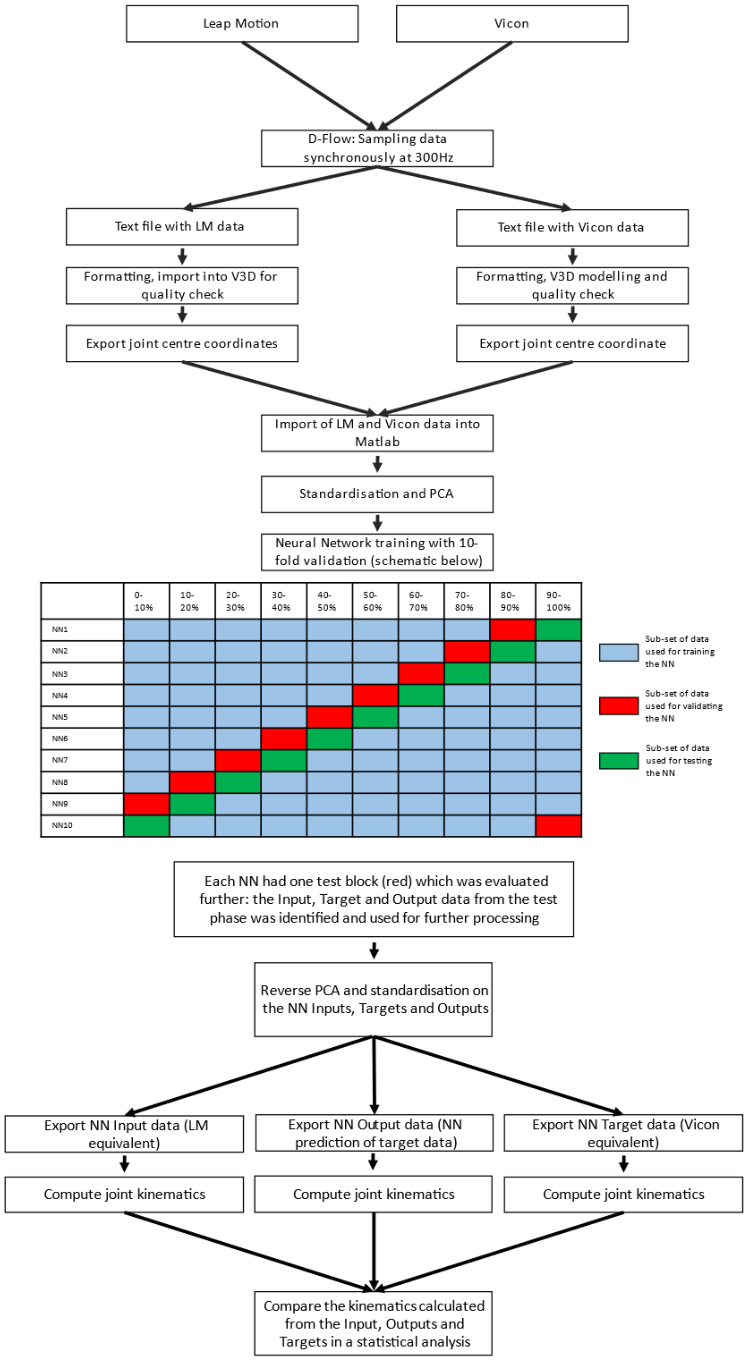

Figure 21: A schematic representing the stages of data acquisition, processing, neural network stage, and subsequent data analysis. See further details described in the main text.

6.4. Results

The application of the artificial neural network reduced the error of the LM when compared to the gold-standard opto-electronic Vicon measurements, however several discrepancies between both LM to Vicon and NN to Vicon were identified.

6.4.1. Correlation analysis

For the random hand movement analysis, correlations between the NN prediction and Vicon data (output and target respectively) were stronger and more frequently significant than the correlations between LM and Vicon data (input and target respectively) across all 10-folds of all NNs, apart from NN4 (Figure 22 and 23). In general, this reflects a greater linear agreement of the angles calculated from NN prediction and Vicon data, when compared to angles calculated from LM and Vicon data.

Most correlations between both LM and Vicon and NN output and Vicon were identified to be significant for the random hand movements as indicated by the p-value (Figure 22). The task and hand specific neural network analysis (Appendices 3-5) are also largely significant, with most insignificant correlations found for thumb circumduction of the left and right hand. Most significant correlations are marked '0' in the table indicating a p-value < 0.01. As significance of correlation does not indicate the strength or direction the R value were examined.

Despite the correlations between the data sets being significant, the strength of the correlations (for random hand movements) between the LM and Vicon data prior to NN application shows a large range from strong negative (R = -0.88) to strong positive (R = 0.95), with the majority of angles showing a moderate to strong positive correlation (mean R value: 0.58) (Figure 23 a). The correlations between the NN output and Vicon data is slightly stronger on average (mean R value: 0.60), as indicated by the change in

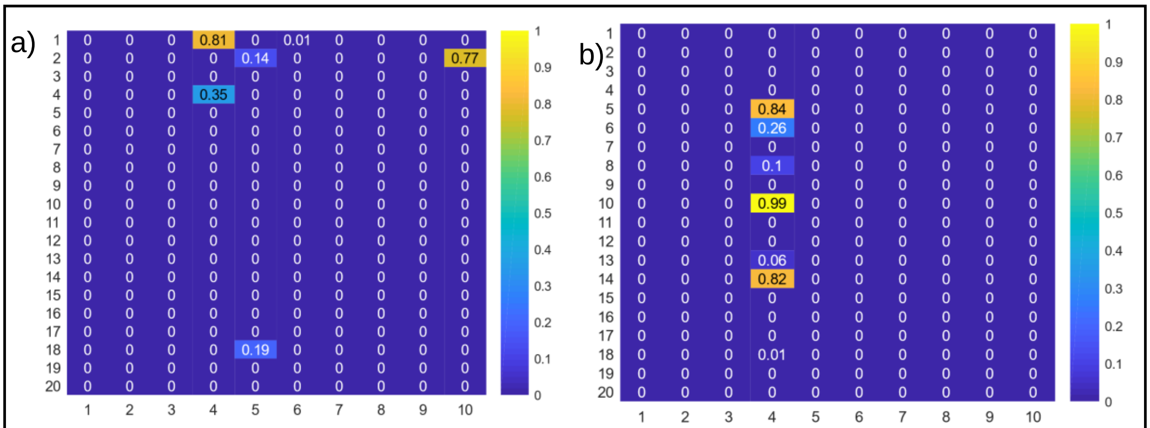

Figure 22: p-values for the correlation between (a) LM and Vicon data and (b) NN output and Vicon was significant for most angles (y-axis, angles labelled using numbers outlined in table 4) and 10-fold validation sets (x-axis) for the random hand movement analysis. The NN output (b) showed significant correlations with the Vicon data across all joints and NNs apart from NN4 which was the weakest NN of the 10-fold validation.

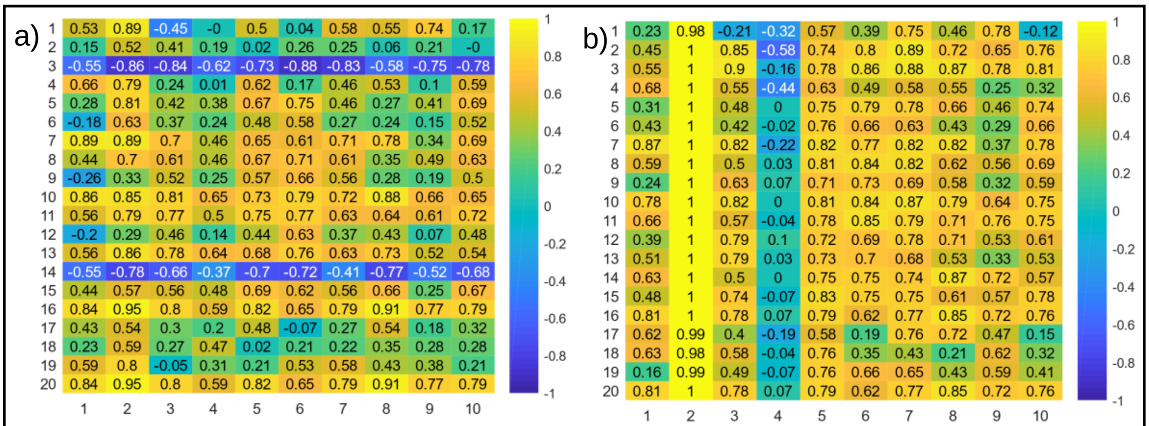

Figure 23: The correlation coefficient (R) for the random hand movement analysis showed very variable correlations between the LM and Vicon (a), ranging from -0.88 to 0.95. On average the correlations are moderate to strong for the LM and Vicon comparison (144 (out of 200) R > 0.30 (moderate) and 45 R > 0.7 (strong)). The NN output to Vicon correlation (b) showed perfect or almost perfect agreement for the second data fold (x-axis) (R = 1), and no to weak correlation for the fourth data set. In general, as indicated by the change of shading, the NN was able to increase the R value compared to the LM to Vicon correlation (more yellow in b) compared to a)).

shading of the colourmap (Figure 23 b). This trend of stronger, positive correlations between NN output and Vicon data compared to LM and Vicon data is consistent across the additional task specific movements for both hands apart from the thumb (Appendices 3-5). The LM to Vicon correlations are typically weaker, but also more consistent between the 10-fold data splits (1-10) than the NN prediction to Vicon correlations. Not all NN models are equally good at predicting target data confirmed by the differences in p-values and correlation coefficients across the 10 folds. For random hand movements, the second data set (NN2 on x-axis of Figures 22-23) shows highly significant (all $p < 0.01$) and perfect ($R = 0.98$-1) correlations. For the same analysis, the fourth data split (4 on x-axis of Figures 22-23) shows several insignificant ($p > 0.05$) and weak ($R = -0.33$-0.7) correlations. Similar differences were identified for the task and hand specific NNs (Appendices 3-5). The flexion-extension tasks (Appendix 3) showed bilaterally good correlations between for flexion-extension angles (rows 1-15) and weaker correlation for the abduction-adduction angles (row 16-20). Similarly, the abduction-adduction tasks (Appendix 4) showed strong correlation for the abduction-adduction angles (row 16-20), but generally poorer agreements for the flexion-extension angles (rows 1-15). The thumb circumduction tasks (Appendix 5) showed bilaterally the most insignificant and poor correlations, including the primarily moving joints of the thumb, thus contradicting findings of the other task specific assessments.

6.4.2. Root Mean Square Error

The correlation analysis explores linear relationships, yet that does not essentially mean a perfect agreement of the magnitude of data points. Therefore, the root mean square error (RMSE), reflecting the mean difference of the amplitude between the LM and Vicon curves (Figure 24 a) and NN prediction and Vicon (Figure 24 b) were examined. An RMSE of zero would reflect a perfect overlap between the two data curves and the greater the RMSE, the greater the distance between the values.

For the random hand movement analysis (Figure 24 a+b), the RMSE is on average greater for the LM to Vicon data (18.99° ± 8.45), compared to the NN prediction to Vicon data set (7.72° ± 4.48). Therefore, the percentage change (Figure 25) is found to be negative for most angles and data splits. However, in some cases the NN method led to higher RMSE values compared to the LM data (Figure 25 positive percentage change reflecting an increase in RMSE). The changes in RMSE support previous

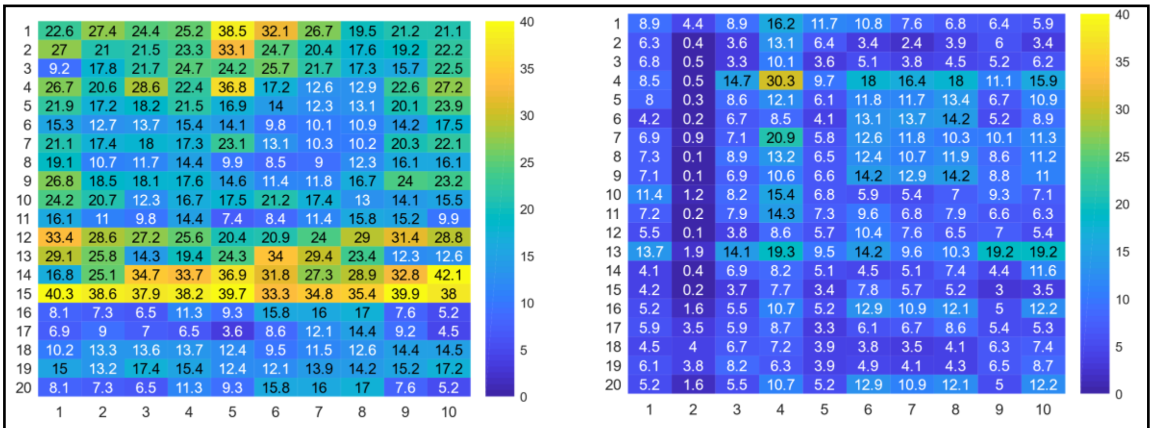

Figure 24 : The RMSE was calculated for each joint angle between (a) LM and Vicon and (b) NN output and Vicon across all 10 folds for the random hand movement analysis. As indicated by the change in colour, the RMSE was reduced by the NN method when comparing RMSE values of the (a) LM to Vicon and (b) NN and Vicon.

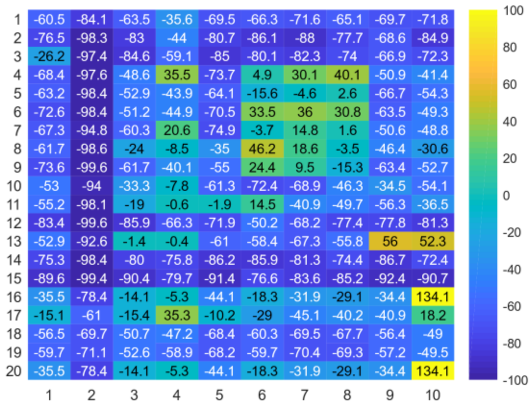

Figure 25: The table shows the percentage change between the LM to Vicon RMSE and the NN Output to Vicon RMSE for random hand movements. The NN was able to reduce the RMSE in most joints as indicated by a negative number, but in some cases the NN induced greater errors compared to the LM (positive number). No pattern was identified that could predict the overestimation of angles by the NN.

findings of changes in strength of correlation, as assessed with the correlation coefficient (Section 6.4.1.), and again show differences between the ten data sets used during the 10-fold validation. All original data was checked carefully for quality, however, slight rotation of the wrist of scaling of the skeletons (hand dimensions did differ between participants) could have influenced these results. In general, the pattern identified for the random hand movements presented here was similar to the patterns identified for the task and hand specific hand movements (Appendices 3-5). The flexion-extension and abduction adduction tasks showed stronger correlations for the

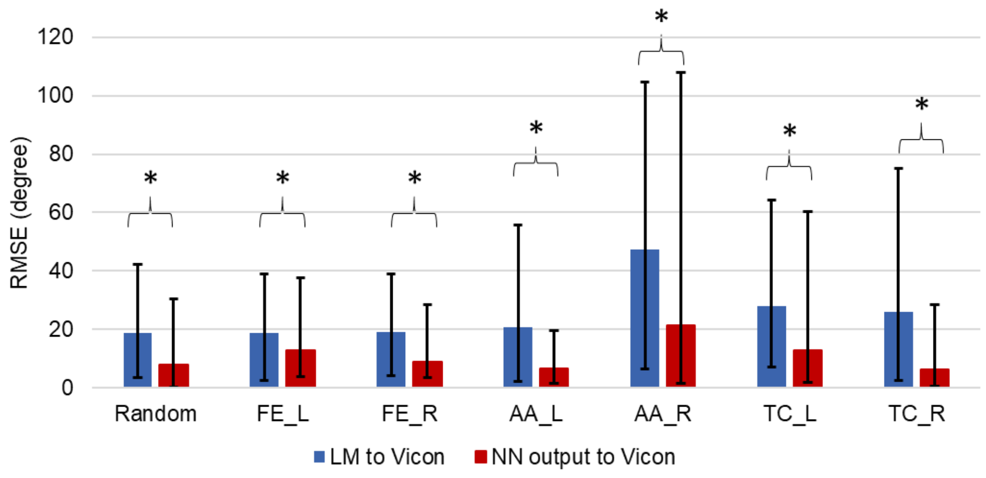

Figure 26: The average RMSE was significantly reduced between NN output and Vicon compared to LM and Vicon (TI) for random hand movements (random) and abduction-adduction (AA), flexion-extension (FE) and thumb circumduction (TC) of the left (L) and right (R) hands. The average error reduction across all joints and 10-folds was calculated. The TO RMSE was found to be significantly lower than the TI RMSE of each analysis. Data shows as mean ± the range.

predominantly moving joints through the respective directions (flexion-extension angles (row 1-15) and abduction-adduction angles (row 16-20) respectively) and worse predictions for the non-targeted directions, suggesting that NNs are more able to predict one movement direction at a time. This is further supported by low RMSE values for those angles across all then data splits (Appendices 3-5). The thumb circumduction analysis resulted in similarly varied results as the random hand movement analysis for the RMSE and subsequent reduction or increases in RMSE when comparing the two approaches.

On average the NN significantly ($p<0.001$, Figure 26) reduced the RMSE for random hand movements as well as all task and hand specific movements between 31-75% (Random: 58.52%; FE_L: 31.19%; FE_ R: 53.74%; AA_L: 67.35%; AA_R: 54.84%; TC_L: 54.64%; TC_R: 75.29%) and thus the NN improved the agreement between the LM and Vicon angles. However, the angular kinematics predicted by the NN are not entirely in agreement with the gold-standard Vicon data. Further, not only the overall RMSE was reduced but also the range and SD, suggesting the LM data corrected by the NN to be more consistent than the LM on its own. It appears that movement specific tasks are more accurate at assessing the movement range of the primarily moving joints.

6.4.3. Angular magnitudes

The correlation and RMSE analysis was used to assess the overall quality of the methods. In a final step the angles calculated from the LM, Vicon and NN output data were plotted against each other to visualise the difference over time. Given the large data set, only a subset of data is shown in this thesis. For random hand movements, it was previously shown that not all neural network models were equally able to predict Vicon data. While the second one shows perfect correlation, the fourth is a lot weaker. This is possibly linked to the input data, as the movements might be unique in range and orientation (NN4) or show only small ranges with a highly repetitive movement pattern (NN2). The remaining eight NNs demonstrate the anticipated pattern of NN quality. Examination of sample frames of the eighth data split of the random hand movement assessment (Figure 27) regarding the angular output shows poorer agreements between the LM and Vicon curve compared to NN predicted and Vicon angle curves. The LM curves do show only a slightly different pattern than the Vicon curves, but at a greater offset, which explains the greater RMSE values despite similar mean R values across all 200 comparisons. Interestingly, this pattern was also frequently observed during the task and hand specific assessments (Appendices 3-5). The only slightly different pattern of the LM angles compared to the Vicon data explains the largely significant and moderate to strong correlation. The offset explains the higher RMSE values. The NN prediction is a bit more irregular, as for some occasions the NN prediction highly accurately matches the Vicon data, whereas irregularly it overestimates the magnitude leading to large errors despite regular patterns in the Vicon and LM data. Overestimating angular magnitudes increases the error relative to the LM. The reasons for these irregular predictions cannot be explained at this stage, which would be critical to establish a consistent and reliable neural network model.

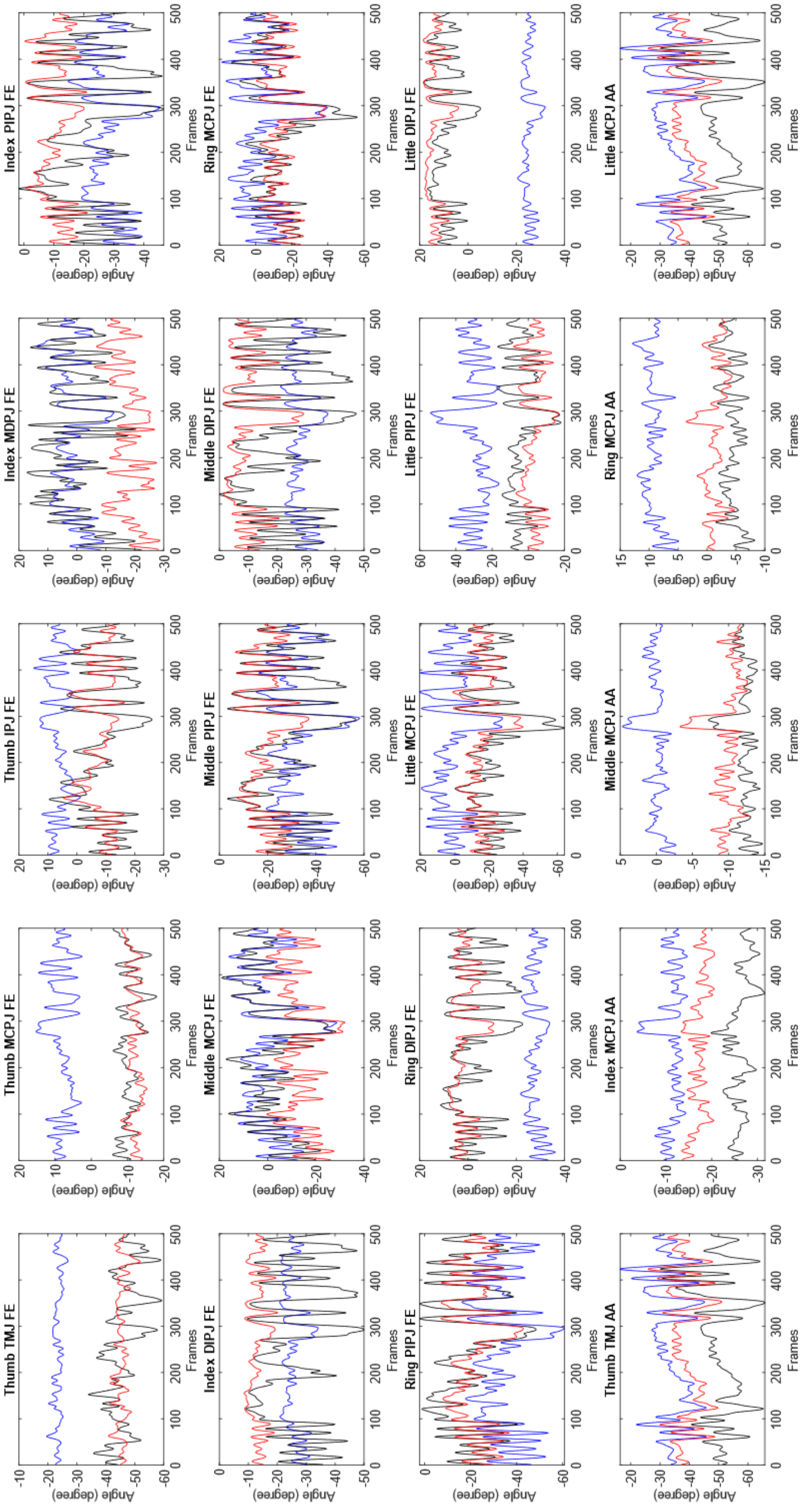

Figure 27: Finger joint angles (°) for random hand movements. The data shown is a sample (Frames 1 - 500) of the eight data set (NN8), which showed weak to moderate correlations and average RMSE values for both LM (blue) to Vicon (black) and NN prediction (red to Vicon (black) comparisons. Despite average agreement between, the NN shows great overlap with the Vicon data, yet sometimes presents at a greater distance than the LM data. The LM data (Blue) shows greater offset to the Vicon (black) data on average, while the pattern is again similar. This angle plot therefore is consistent with the findings of the correlation and RMSE analysis. This plot further illustrates the differences of NN models to accurately predict Vicon data.

6.5. Discussion

The results indicate a 31-75% error reduction on average for the individual tasks assessed as validated by a 10-fold cross-validation. Yet large, irregularly occurring discrepancies between the NN prediction and Vicon target data were identified. The LM data showed worse results for the correlation and RMSE, yet the curves look relatively similar in shape, but are offset by multiple degrees.

The LM alone is inaccurate when measuring dynamic hand movements using angular kinematic profiles. While it was known that the ROM measurements are inaccurate (Nizamis et al., 2018), this study measured dynamic movements. Our findings therefore enhance and support current literature findings regarding the LM accuracy. It appears though that the LM has a large systematic error, which would explain the offset relative to the Vicon curve. A simple offset calculation (Ferrari et al., 2014) would already reduce the error between LM and Vicon data, which in turn is in agreement with the finding of the original pilot work (Appendix 7).

Most correlations, for both LM to Vicon and NN prediction to Vicon, were significant at a level of $p<0.01$. Yet the correlation coefficients showed often weak or moderate correlations despite significant interactions. If plotted, the correlations show a heteroscedastic spread. Heteroscedasticity tends to lead to small p-values (smaller than under homoscedastic spreads), because heteroscedasticity means higher variance of the correlation coefficient. This could also explain the ceiling effect observed for the p-values in all seven neural network assessments. Simultaneously the heteroscedastic spread of data explains the highly variable correlation coefficients observed in this study. Heteroscedasticity is typically associated with outliers in the variables, yet no outliers were identified in the original data set. It is important to acknowledge that based on the visually assessed angle data, the LM does collect data at an offset, yet in particular at the end points of the range errors are more likely. Correlations assess linear agreement, yet the LM does show a non-linear error, which was partially reduced by the NN application. Therefore, the NN to Vicon comparison showed improved correlations compared to LM to Vicon, despite a heteroscedastic spread observed for the correlations between the NN prediction and Vicon target data.

The NN was able to partially correct the non-linear error of the LM, yet often also increased the RMSE. Based on the data presented in this study, the reasons for this are unclear as sudden changes in the NN prediction also appear when the original input (LM) or target (Vicon) data lack steep changes in the data. Further the ability of accurately predict Vicon data varied greatly among the 10 folds. The inconsistencies of the current artificial neural network may suggest unreliable results if these models are applied to data from new subjects such as patients.

The thought that a movement and hand specific NN model could improve the NN ability to predict Vicon data accurately was only partially accepted. Whole hand movements were not well predicted, however, the angles of movements (FE angles during flexion-extension movements and AA angles during abduction-adduction movements) were measured well with the LM and showed strong correlations and low RMSE when compared to Vicon data. These were further improved by the NN approach. Unfortunately, this finding was not supported by the thumb circumduction trials, which might indicate some more fundamental issues with thumb movement data in either the LM or Vicon motion tracking.

There were fewer data points available for the NNs trained for specific movements and tasks compared to the random hand movements, which might have skewed the results. The quantity of data points is a critical factor when designing neural networks. While there is no ‘one size fits all’ answer to the quantity of data required it is suggested that a neural network predicting complex patterns requires more training data than a simple task. Hand movements are very complex, therefore larger data sets for training, including data from a wider age-range given that hand movements change with age would be useful and could possibly improve the results of this study.

The use of the LM for motion analysis provides a portable, easy to use alternative to a marker-based motion capture approach, such as the Vicon system, therefore allowing the assessment of movement impairments of clinical cohorts, such as patients with SSc, in the field, or the patient's home (Chapter 7). The LM could further aid the translation of research into clinical practice to measure the progression of the disease over time for example by using the MDP and MDP_{mean} (Chapter 4). Further, given the good correlations between LM and Vicon data, despite large RMSE values, the LM could be used to play VR games, such as the FlappyBall game (Chapter 5), which is driven by the range and position of fingers within the measured range rather than absolute angle data. Further, the strong correlations allow the LM to be used to determine changes over time. While the absolute measures might be at a distance the gold-standard measure, it is thought that this is linked to a systematic error. Thus the change over time, if measured with the LM at both occasions, can still be assessed. The NN approach shows some promising results, however is at this stage not ready for application. Once the reason for inconsistent predictions has been identified and a solution has been provided, the NN approach could aid the accurate assessment of motion to gold-standard levels. Yet, absolute angles to gold-standard levels are not always required, depending on the study design.

For this study, 15 young, healthy adults were recruited for each of the two parts. The responsiveness of the LM and developed NNs to hand deformities or movement limitations is unknown. It is possible that hand deformities and movement impairments are not correctly predicted by this method. Therefore, this protocol and the current NN training database needs to be applied to and enhanced with patient data.

Future research should first of all identify the reasons for the mixed predictions of the neural network and how to overcome these. Further the use of deep-layer artificial neural networks in addition to time-series machine learning protocols could be considered given the time-series data and unequal sampling methods. More complex

NNs could potentially improve the prediction of complex hand movements in all dimensions due to the increased number of neurons and could potentially avoid overestimation of joint parameters. Further, more data should be acquired to enhance the data set as increasing the quantity of data points for NN training improves the rigidity of the NN approach. Measuring full flexion range with the marker-based approach was not possible, therefore only 75% of the flexion range was measured. It is uncertain how the NN would perform upon fist closure.

6.6. Conclusion

The error of the kinematic movement data generated with the LM was significantly reduced on average after the application of the NN. While this is a positive indicator of the NN approach to reduce the error, the NN predictions were largely inconsistent among the 10 folds and showed several large, sharp changes in the angle data. Therefore, at this stage the NN approach shows some very positive results but due to the inconsistent ability to predict data it cannot be used for clinical applications. On the other hand, the LM was considered to be inaccurate. While this is true when assessing absolute differences between Vicon and LM angle curves, the shape of the curves was similar but at an offset, and the correlations where found to be frequently between moderate to strong. Especially for movement specific tasks the LM showed very good agreement for the primarily moving joints, suggesting that the LM can be used for research, but only if clear movements in one direction are performed, such as when playing the FlappyBall game (Chapter 5). Further the RMSE between LM and Vicon is largely affected by the offset which is due to a systematic error. Therefore, the LM can be used as a standalone tool for motion analysis, but the generated data cannot be directly compared to marker-based motion capture approaches and needs to be interpreted with caution.

Chapter 7: Virtual Rehabilitation vs. Physiotherapy: A comparison of two rehabilitation approaches on hand function in patients with systemic sclerosis

Thesis structure				
Chapter	Title	Structural design	Addressed Aims	Linking to Chapters….
3	Describing the development of an opto-electronic and a markerless motion capture approach for the hand and subsequent kinematic modelling	Developmental study: Technical chapter outlining the design of kinematic models used in this thesis		4, 6 and 7
4	A comparison of hand movements during functional tasks in patients with systemic sclerosis and age- and hand dominance-matched healthy controls	Experimental study: Comparing hand movements of patients with SSc to age-matched healthy controls to quantify joint specific movement impairments	**Aim I:** Accurately assess the hand movement limitations of patients with SSc during functional tasks using three-dimensional motion analysis	5 and 7
5	Method chapter: Design of a virtual rehabilitation game for systemic sclerosis informed by three-dimensional movement analysis	Developmental study: Technical chapter with a detailed description of the design of a virtual rehabilitation tool for patients with SSc	**Aim III:** Deploy the portable motion capture method into a virtual rehabilitation context	7
6	Improving the accuracy of the Leap Motion controller for purposes of markerless hand motion capture using artificial neural networks	Experimental study: Assessment of the Leap Motion controller to accurately measure hand kinematics before and after the application of neural networks in comparison to an opto-electronic measurement approach.	**Aim II:** Develop a portable method to capture 3D movement	7
7	Virtual Rehabilitation vs. Physiotherapy: A comparison of two rehabilitation approached on hand function in patients with systemic sclerosis	Experimental study: RCT comparing the effect of two intervention programmes to improve hand function in patients with SSc	**Aim IV:** Examine the effect of the virtual rehabilitation tool in comparison to traditional physiotherapy on hand movement limitations	3, 4, 5, 6

7.1. Preface

Chapter 4 assessed movement impairments in patients with SSc using a gold-standard motion capture approach. It was identified that impairments are evident at all joints and directions of movement. This information was then translated into a virtual rehabilitation game (Chapter 5), which allows for the training of flexion-extension and abduction-adduction mobility in a dynamic, active range of motion, multi-joint approach. Conventional therapy typically involves passive hand stretches and grip strength exercises, largely focussing on finger flexion. Whilst these exercises show beneficial effects for hand function, they are perceived as boring and adherence to these programmes is low. Virtual rehabilitation could possibly increase adherence, however, there is currently no evidence of the beneficial effects of virtual hand exercises in patients with SSc. Therefore, the **aim** of this chapter was to assess the effects of game-based virtual rehabilitation exercises on finger mobility, finger dexterity and ability to perform ADLs independently in comparison to the conventional physiotherapy approach. To measure the effect of the exercises a motion analysis, motor control test and Finger-to-Palm index in addition to patient-reported outcome measures was taken before and after exercises as well as after four weeks without exercises. The changes across all tests were then compared before and after the intervention and between groups to determine if one intervention showed a greater effect than the other. It is hypothesised that both exercises show positive changes across all measures, whereby the virtual rehabilitation group is expected to show greater beneficial effects and higher levels of enjoyment.

7.2. Introduction

The hands are integral to our daily lives as we use them for daily leisure and work activities. In the presence of hand impairments, the ability to perform ADLs is reduced, leading to social isolation, depression and anxiety. The psychosocial effects enhance the physical effect of reduced hand mobility, leading to a reduced level of independence and quality of life (Maddali-Bongi et al., 2014; Mao and Sun, 2014; Nguyen et al., 2014; Rannou et al., 2007). Patients with SSc present with impaired hand function, and they frequently report poor mental health, as well as feeling uncomfortable in public and dependent on help from others. The disease burden therefore is not only of physical nature but also involves a psychological component. Negative attitude or grief due to the knowledge of having an uncurable disease can influence physical factors and tendency to socially isolate and depend more on others than needed (Bolden, 2010). Effectively the interplay between psychosocial and physical factors can lead to a downward spiral, which could be prevented by an effective rehabilitation programme for the hand. The aim of rehabilitation programmes is typically to increase the range of movement, which is associated with an increase in ability to perform ADLs, independence and reduced movement-induced pain (Rannou et al., 2017).

Traditional interventions, including hand stretches and strength exercises are recommended by healthcare professionals as well as systemic sclerosis societies (Scleroderma and Raynauds UK, Scleroderma Foundation (USA), Scleroderma Australia, DNSS (Germany)). Several studies reported an improved hand function after a prescribed exercise programme in regards to movement range and patient-reported improved ability to perform ADLs (Antonioli et al., 2009; Horvath et al., 2017; Maddali Bongi et al., 2009; Poole et al., 2013a; Poole et al., 2013c; Rannou et al., 2017; Stefanantoni et al., 2016). To the author’s knowledge, no study measured joint specific range of motion of each finger joint to objectively assess the mobility changes induced by an intervention programme.

Despite promising results from the literature regarding the effectiveness of exercises, referral to exercise schemes is only done for less than half of the patients, and only approximately 12% of the referred patients enrol in a programme (Bassel et al., 2012; Willems et al., 2015a). Adherence barriers, as described by patients with SSc are similar to barriers described by sedentary healthy individuals to physical activity. Most patients state a lack of time, difficulty to prioritise and a disbelief of the beneficial effect of hand exercises. While the first two barriers are linked to personal commitment and motivation, the latter can be addressed through education and possibly experience after engaging in exercises in the first place.

For this to happen, a rehabilitation approach which minimises the burden, and improves adherence is required. A virtual rehabilitation tool was created in previous work (Chapter 5), which could potentially raise motivation to complete exercises in a playful environment, thus mimicking a reduced burden of the exercises. The beneficial effects or virtual rehabilitations has been demonstrated in several conditions and research studies (Barton et al., 2013; Bryanton et al., 2006; dos Santos Mendes et al., 2012). Virtual rehabilitation was applied in mostly neurologically impaired patients. Following a training phase, range of motion as well as motor control was improved as the participant learned to control their movements. Patients with SSc are considered to be neurologically unimpaired, but it is known that the neural control over movement is gradually lost if the musculoskeletal system is not actively used, yet can be re-gained with training (Gabriel et al., 2006; Nordin et al., 2017). In a previous study, we further suggested that finger dexterity could be reduced in patients as they required a significantly longer time to complete functional tasks (see chapter 4). To the best of the author’s knowledge, no study has yet examined finger dexterity in patients with SSc. Finger dexterity and ability to perform ADLs was found to be positively correlated, and an improvement of dexterity has a larger impact on the quality of life than the range of motion. We therefore hypothesize that, if SSc patients do experience a loss in dexterity, training on a virtual rehabilitation game which trains range and dexterity, will have a greater beneficial effect compared to conventional therapy in form of hand stretches.

The aim of this study was to evaluate the effectiveness of virtual rehabilitation compared to standard physiotherapy exercises on patient-perceived functionality of the hands, objectively measured hand mobility as well as finger dexterity. Secondly, we evaluated the level of engagement and likelihood of adherence to the prescribed programme.

7.3. Methods

This study was designed as a randomised control trial to assess the effect of virtual rehabilitation (VR) on hand function in patients with SSc. This study was approved by the National Health Service Research Ethics Committee and Health Research Authority (IRAS: 248310; REC reference: 18/NW/0659).

7.3.1. Participants

Twenty participants diagnosed with SSc (EULAR/ACR score >9, without longstanding flexion contractures, 54.8 ± 23.1 years; female: n = 19, male: n = 1) were recruited from the rheumatology department of a local hospital. The presence of active ulcers or calcinosis at approach or upon enrolment led to exclusion from the study. Participants were not enrolled in any other intervention study (neither pharmacological, nor non-pharmacological), nor did they receive any other physical or occupational therapy treatments for the duration of this study and at least eight weeks prior to enrolment. Out of 20 enrolled patients, 18 completed the study (dropout: n = 2), whereby one participant of the intervention and control group each did not complete the training and follow-up test protocols.

Following block-randomisation (block size: 5), the VR group was composed of nine females and one male and included three dominant left-handed and seven right-handed patients. Half the participants were diagnosed with dSSc, the other with lSSc. Out of the ten patients nine were tested positive for ANA autoantibodies, two for anti-topoisomerase, and six for anti-centromere. On average this group was 53.4 ± 11.6 years old, had a mean time since diagnosis of 14.3 ± 5.7 years, and a modified Rodnan Skin Score (mRSS) of 9.5 ± 5.5.

The physiotherapy group included ten females, whereof two were dominant left-handed and eight right-handed. Half the patients were diagnosed with dSSc and the other half with lSSc. Nine patients are ANA positive, three anti-topoisomerase positive and four showed anti-centromere autoantibodies. On average this group was 58.6 ± 9.8 years old, had a mean time since diagnosis of 10.1 ± 5.0 years, and a mRSS of 9.3 ± 6.6.

As both classification of the disease as well as antibody status are linked to movement impairment it is important to note that both lSSc and dSSc, as well as the antibody types present in the patients were balanced and comparable between the groups. Further the mRSS, indicating skin stiffness on the whole body was comparable between the groups.

7.3.2. Trial design

The trial design, as well as design of intervention tools, followed the TIDieR checklist (Hoffmann et al., 2014), and the domains are appropriately highlighted throughout this chapter. The physiotherapy group followed a conventional exercise programme based on hand stretches. Both groups spent the same amount of time (90 minutes per week) on their exercise programme, which was conducted entirely at the patient's home for both groups typically on the kitchen table or office desk (TIDieR Domain 7). The study duration was eight weeks, split into two four-week blocks: in the first four weeks participants performed exercises, whereas in the second four-week block exercises were discontinued to quantify the retention of changes in functionality (TIDieR Domain 8). This level of intensity and duration is consistent with several exercise studies in systemic sclerosis. Objectively measured range of motion, patient-reported ADL performance and hand function, as well as dexterity were assessed at baseline, after four weeks of exercises (Day 28) and further four weeks without exercises (Day 56) (Figure 28). Participants were randomly allocated to the intervention or control group using block-randomisation (block size: 5). Participants were informed that we were comparing two rehabilitation programmes without any clear hypothesis or expectation for the result in an attempt to blind the study, reduce bias and the Hawthorne effect.

Figure 28: Trial structure. Of all participants baseline data was collected upon enrolment (Day 1), which was followed by a four-week exercise block. The participants were allocated to one of the two groups and completed their respective exercises three times per week. After four weeks of training all test protocols were repeated (Day 28). The second test session was followed by a second four-week block, and this time participants from both groups were instructed to not perform any exercises. On day 56 all measurements taken at baseline were repeated again.

7.3.3. Rehabilitation programmes

Two programmes for hand rehabilitation in patients with SSc were designed for this study for comparison. The VR programme is a novel approach for joint stiffness in SSc, and is compared to conventional exercises which are frequently suggested by charities, health bodies and hand therapists.

7.3.3.1. Virtual rehabilitation

Participants of the intervention group played a customised computer game (for details see: Chapter 5) three times a week for 28 minutes (14 minutes for each hand). The participants played the game for seven minutes, split up into 7 x 1 min bursts, using their flexion-extension range, followed by seven minutes to train abduction-adduction movements. When playing the game, participants were in seated position, holding their hand approximately 25 cm over the controller, with the shoulder flexed at approximately 45°. A wrist support was provided to standardise the distance and for comfort of the participants. The training sessions were supervised by a skilled researcher, which also aided the monitoring of adherence to exercise programme as well as the monitoring of performance of the correct movement throughout the training phase (TIDieR Domain 11). The researcher would correct the participants movement using verbal feedback to ensure the movement which was targeted was correctly performed and therefore allow the game to respond accordingly. This was mostly to provide the equipment and operate the game. The game was introduced and briefly verbally explained to the participant prior to the first trial. During the verbal explanation the goal of the game and movements to drive the game were explained. The participants then actively tried the game and learned from the visual feedback in the game how to control movements of the ball through the obstacle course. After the first trial, the participant could ask any questions, and the researcher explained the error scoring, timing and movement to drive the game. Throughout all sessions, verbal encouragement from the researcher was kept to a minimum. The computer game settings were set to match the patient's ability at the beginning of each session. All participants started their first training session with the default settings described in Chapter 5. Settings were never changed in the course of a training session. If a participant got less than three errors on three consecutive trials, the difficulty settings were adjusted in the next training session. Only one parameter was adjusted at a time in the order prescribed by the game design (see Chapter 5).

7.3.3.2. Physiotherapy exercises

The hand exercises used were taken from multiple sources. For this study we reviewed exercises from the NHS, Scleroderma and Raynaud's UK, The Salford Royal NHS Hospital, The British Association of Hand Therapists and multiple published exercise intervention studies in SSc. In total 15 exercises were chosen (see Table 6) and composed in a leaflet (TIDieR Domain 3). The leaflet was handed to the participants of this group, alongside any equipment needed. During the first supervised face-to-face session, a member of the research group (TIDieR Domain 5) carefully explained all exercises, familiarised the patient with the equipment and introduced the patient to the training diary (TIDieR Domain 3). To ensure the participant fully understood the procedures awaiting, the first training session was completed and diary filled in together. After one supervised training session, the remaining 11 sessions were self-managed (TIDieR Domain 4 and 6). The participants of this group received weekly phone calls for the duration of the training phase to track progress, adherence and answer any questions the participant had (TIDieR Domain 6). In their diary participants recorded the exercises completed in a session, as well as the duration and number of repetitions of each task on each hand (TIDieR Domain 11). The diary also had a contact list attached in case of any urgent study related questions or medical emergencies that could have been induced by the exercises. No specific modifications and tailoring to individual ability was done for this study group, instead participants were instructed to push their ability their perceived limit in every exercise session (TIDieR Domains 9 and 10).

Table 6: Hand exercises performed by the control group three times per week.

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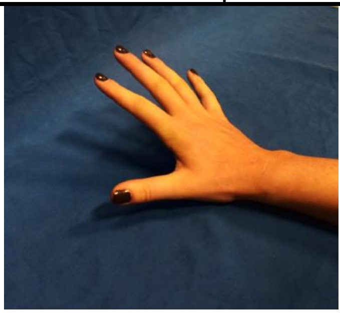
<td>
<u>Exercise 1</u>: Lifting all fingers from the table thereby getting the fingers as straight and wide apart as possible. The wrist was slightly extended. Hold for 3 x 10 seconds, repeat on both hands.</td>
<td>
<u>Exercise 2</u>: Lift every finger individually while keeping the wrist and palm on the table. Hold for two seconds on each finger, repeat three times per hand.</td>
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<td>
<u>Exercise 3:</u> Put your hands above one another on a flat surface. Gently push down your lower hand with the upper hand and hold for ten seconds. Repeat three times on each hand.</td>
<td>
<u>Exercise 4</u>: Tap the thumb with the index, middle, right and little finger and briefly squeeze together. Repeat three times on both hands.</td>
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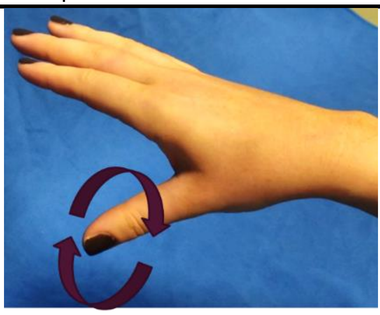
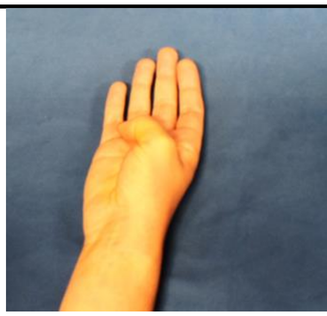
<td>
<u>Exercise 5</u>: Draw a circle in the air with your thumb, stretching your thumb as much as you can. Draw five circles, and repeat three times per hand.</td>
<td>
<u>Exercise 6</u>: Place your hand on a flat surface, palm facing upwards. Move the thumb towards the base of the little finger and hold there for five seconds. Repeat three times per hand.</td>
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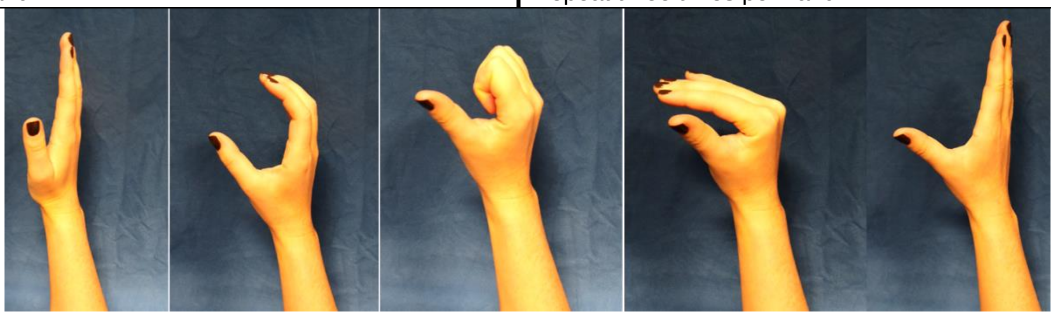
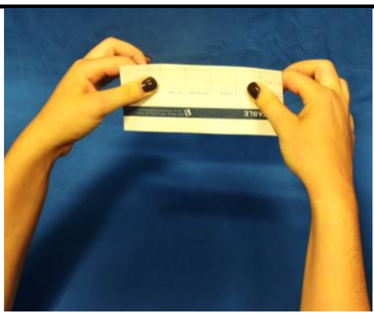
<td colspan="2">
<u>Exercise 7</u>: Rest your elbow on a table and hold your hand as straight as possible. Bend the two top joints. Then bend the knuckles followed by extending the top two joints but keeping the knuckles bent. Then form an L with your thumb. Hold each position for five seconds. Repeat three times per hand.</td>
</tr>
</table>

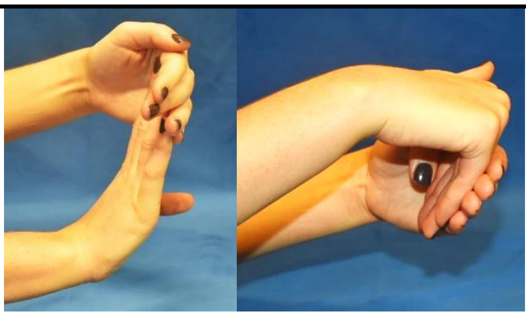
Exercise 8: The hand is on a flat surface, fingers spread apart maximally. Hold for five seconds. Repeat three times per hand.

Exercise 9: Interlock your fingers and hold for ten seconds. Repeat three times.

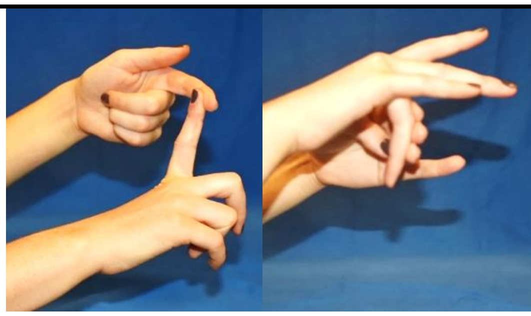


Exercise 10: Pick up a piece of paper and pinch it between the thumb and index finger. Repeat three times.

Exercise 11: Pick up a coin from a flat surface and pinch it between the thumb and index finder. Repeat three times on each hand.

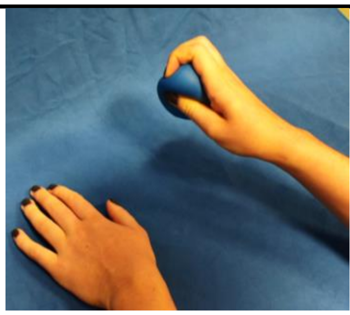


Exercise 12: Pull all fingers of one hand back with the other hand, then bend thee fingers and pull down. Hold 15 seconds in each direction. Repeat three times per hand.



Exercise 13: Pull index finger back using the other hand, then pull down. Hold five seconds in each direction, then repeat on middle, ring and little finger. Repeat three times per hand.

Exercise 14: Place one hand behind the other. Bend and squeeze the top two joints of the bottom hand with help of the upper hand. Hold for 15 seconds. Repeat three times on both hands.



Exercise 15: Pick up a ball and squeeze. Hold for two seconds. Repeat five times and on both hands.

7.3.4. Assessment methods

A three-dimensional motion analysis using the LM was performed. Data was captured in D-Flow, and angular kinematics were calculated in Visual3D (C-Motion Inc., Germantown, MD, USA) by the model described in Chapter 3. Dynamic movements, from active maximum flexion to maximum extension, and for active maximum abduction to adduction were measured. Thumb circumduction was recorded by instructing the participants to draw a large circle (as large as possible) into the air. Further, the FTP was measured using a simple ruler. Participants provided feedback on their perceived functional status via the CHFS. A dexterity assessment was performed using a customised keyboard. Participants followed a tapping sequence for 15 seconds, increasing in difficulty and complexity over seven levels, starting with a single finger and increasing to include four fingers. The sequences were showing colours matching the colours on the customised keyboard. The tasks (1-6) increased progressively in difficulty by combining one (MC1), two (MC2 and MC3), three (MC4 and MC5) or four (MC6) fingers pressing three (MC1-5) or four (MC6) buttons on the customised keyboard. The participants rested the ball of the hand in front of the keyboard and were instructed to type in the sequence in front of them as fast as possible while avoiding to make mistakes. The number of taps made, tapping speed and errors made were recorded in Matlab R2018a (Natick, WA, USA) and written into a text file following task completion for further analysis. All measurements were taken at baseline (Day 1), after four weeks of exercise (Day 28) and after a four-week no exercise period (Day 56).

7.3.5. Outcome measures

Range of motion of all joints was calculated from three-dimensional movement data. Movement range was assessed for all joints in flexion-extension and for the MCP joints and thumb TM joint also the abduction-adduction range. The scores of the CHFS were recorded as well as the FTP (in cm), as described by Torok et al. (2010). The tapping speed from the dexterity test was calculated as taps/second and the mean performance was calculated. Only data of the dominant hand was analysed as no statistical difference was identified between the dominant and non-dominant hand mobility of the patients of both groups (Appendix 6).

7.3.6. Data analysis

A test for normality was conducted on all outcome measures, indicating a non-normal distribution of all quantitative measures. Therefore non-parametric tests were used to the analysis. Median and interquartile ranges were calculated, and an outlier analysis was performed on the raw data. The data was statistically analysed using a Friedman test for within-group changes between test sessions, followed by a Wilcoxon Signed Rank post-hoc analysis. Between group differences were assessed using the Mann-Whitney U test. The change in ROM (ΔROM) was calculated for each joint between the pre- and post-intervention tests (T1-T2) and post-intervention and follow-up tests (T2-T3). A descriptive analysis was conducted, and a Mann-Whitney U test was performed to assess the between group differences. A qualitative analysis was conducted to summarise the patient feedback on motivation and likelihood of adherence from the non-validated questionnaire applied during the post-intervention test session (T2).

7.4. Results

The effectiveness of both intervention programmes was evaluated using several outcome measures which were analysed separately.

7.4.1. FTP

Both groups could reduce the distance between middle fingertip and palm (Median $\Delta FTP_{Pre\text{-}Post}$: Physio: -0.5 cm; VR: -1.5 cm) after training (Figure 29). While the physiotherapy group could maintain their FTP at follow-up ($\Delta FTP_{Post\text{-}FollowUp}$: 0.0 cm) the VR group did not manage to maintain the flexibility ($\Delta FTP_{Post\text{-}FollowUp}$: +0.5 cm). The within-group Friedman tests showed an significant effect of exercises on FTP for the physiotherapy group but not the VR group. (Physiotherapy: $\chi^2(2)=7.625$, $p=0.022$; VR: ($\chi^2(2)=5.840$, $p=0.540$). However, the Wilcoxon Signed Rank post-hoc test showed a significant reduction of the FTP between the pre- and post-exercise tests in the VR group (p=0.048). The Wilcoxon Signed Rank tests showed no significant between-group differences between test sessions. In the physiotherapy three patients improved the FTP, while the others were able to maintain their score after exercises. In the VR group five participant reduced the FTP, one deteriorated to a higher FTP and three maintained their score when comparing pre- and post-exercise tests. Overall, the gradients of the connected scatter plot indicate more improvement in the participants of the VR group compared to the physiotherapy group.

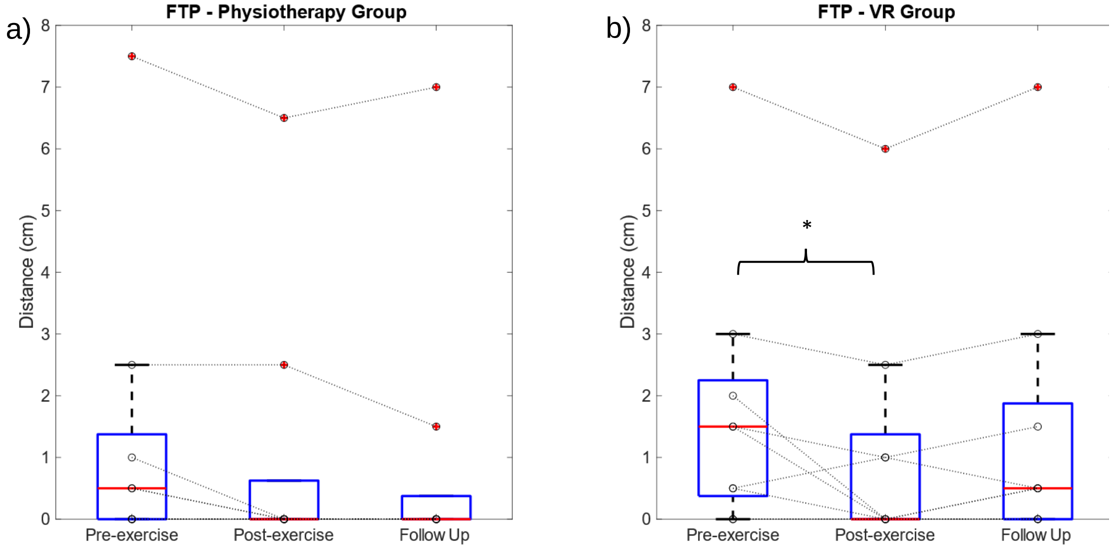


Figure 29: Finger-to-Palm index (FTP) was assessed before (pre-) and after (post-) exercise as well as after four weeks after intervention completion. No significant changes were identified in the (a) physiotherapy or (b) VR group overall. Box-plots show the median ± interquartile range. The whisker length refers to extreme data: if no outlier is present the whiskers extend to the minimum and/or maximum values. In the presence of outliers, the whiskers are equivalent to 1 IQR. Outliers are highlighted in red crosses. The overlaid connected scatter plot shows participant raw data and individual participant changes over time.

7.4.2. CHFS

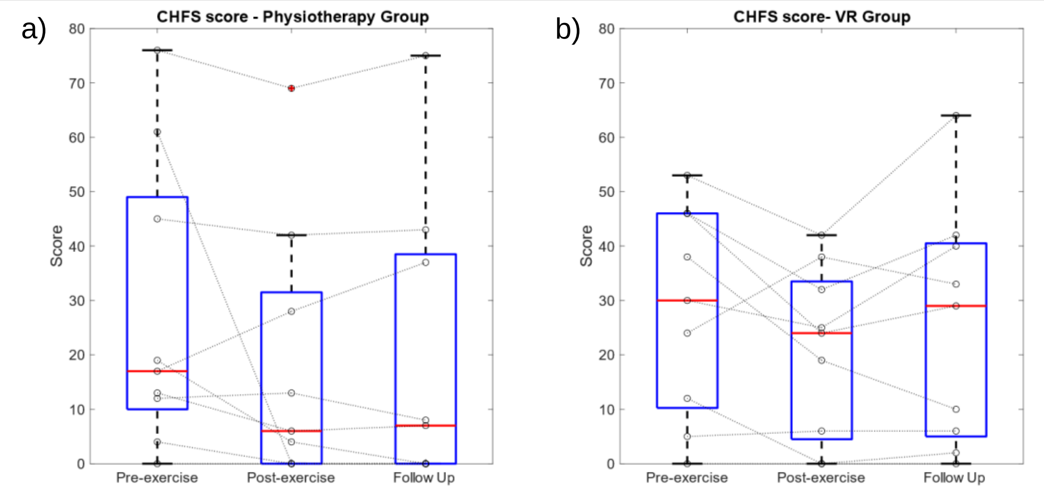


Figure 30: Cochin Hand Function Scale (CHFS) score was acquired before (pre-) and after (post-) exercise as well as after four weeks after intervention completion. No significant changes were identified in the (a) physiotherapy or (b) VR group overall. Box-plots show the median ± interquartile range. The whisker length refers to extreme data: if no outlier is present the whiskers extend to the minimum and/or maximum values. In the presence of outliers, the whiskers are equivalent to 1 IQR. Outliers are highlighted in red crosses. The overlaid connected scatter plot shows participant raw data and individual participant changes over time.

Both groups presented with reduced CHFS scores after training, but these changes were not maintained four weeks after exercise completion (Figure 30). The magnitude of change of the median between pre- and post-exercise results ($\Delta CHFS_{Pre\text{-}Post}$) was -11 (Physio) and -6 (VR) on the scale. At follow-up ($\Delta CHFS_{Post\text{-}FollowUp}$) the scores increased by 1 (Physio) and 5 (VR) respectively. The within-group Friedman tests showed no significant effect of exercises on CHFS score (Physiotherapy: $\chi^2(2)=5.67$, $p=0.079$; VR: ($\chi^2(2)=2.387$, $p=0.303$). The Wilcoxon Signed Rank tests showed no significant between-group differences between test sessions. In the physiotherapy group six patients reduced (improved) the CHFS score, two deteriorated and one could maintain their score after exercises. In the VR group six participants reduced the CHFS score, one deteriorated to a higher CHFS and two maintained their score when comparing pre- and post-exercise tests. Overall, the gradients of the connected scatter plot indicate more improvement in the participants of the VR group compared to the physiotherapy group. However, one participant in the physiotherapy group showed a sizeable 61-point drop on the CHFS after exercises and was able to maintain this drop at follow up.

7.4.3. Finger dexterity

Both groups demonstrated increased median tapping speeds over 15 seconds after exercises across all six dexterity tasks (MC1-6) (Figure 31). In summary, the VR groups showed greater improvements ($\Delta \text{FDex}_{\text{Pre-Post\_MC1-6}}$: +0.20 taps/s, +0.53 taps/s, +0.20 taps/s, +0.46 taps/s, +1.00 taps/s, +0.53 taps/s) than the physiotherapy group ($\Delta \text{FDex}_{\text{Pre-Post\_MC1-6}}$: +0.27 taps/s, +0.14 taps/s, +0.33 taps/s, -0.13 taps/s, +0.27 taps/s,

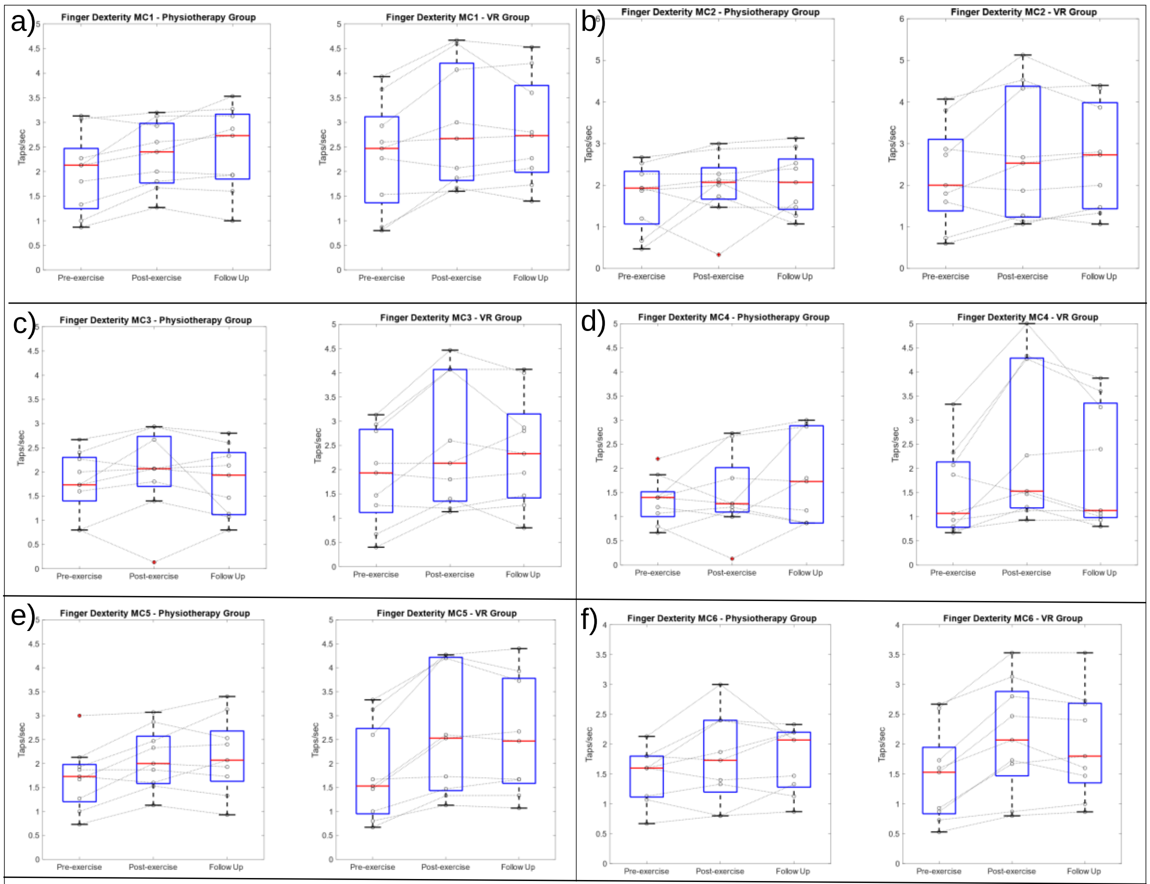


Figure 31: Finger dexterity was measured at six skill levels (MC1-6) (a-f) with increasing difficulty before (pre-) and after (post-) exercise as well as four weeks after completing the intervention programme. Box-plots show the median ± interquartile range. The whisker length refers to extreme data: if no outlier is present the whiskers extend to the minimum and/or maximum values. In the presence of outliers, the whiskers are equivalent to 1 IQR. Outliers are highlighted in red crosses. The overlaid connected scatter plot shows participant raw data and individual participant changes over time.

+0.13 taps/s). The Friedman test in the physiotherapy group showed significant improvements in MC1-2 (MC1: $\chi^2(2)=7.257$, $p=0.27$; MC2: ($\chi^2(2)=1.429$, $p=0.49$), but not MC3-6 (MC3: $\chi^2(2)=6.788$, $p=0.034$; MC4: ($\chi^2(2)=7.118$, $p=0.028$; MC5: $\chi^2(2)=12.514$, $p=0.002$; MC6: ($\chi^2(2)=13.118$, $p=0.001$). The VR group on the contrary showed non-significant changes during MC1-2 (MC1: $\chi^2(2)=11.48$, $p=0.003$; MC2: ($\chi^2(2)=6.059$, $p=0.048$), but strongly significant improvements for MC3-6. The increases in dexterity after exercises could be maintained at follow up and no statistically significant interactions or differences were identified for both the physiotherapy and VR group (Physiotherapy: $\Delta FDex_{Post\text{-}FollowUp\_MC1\text{-}6}$: +0.33 taps/s, +0.00 taps/s, -0.13 taps/s, +0.46 taps/s, +0.07 taps/s, +0.34 taps/s; VR: $\Delta FDex_{Post\text{-}FollowUP\_MC1\text{-}6}$: +0.06 taps/s, +0.20 taps/s, +0.20 taps/s, -0.40 taps/s, -0.06 taps/s, -0.27 taps/s). The VR group showed greater improvements towards more complex tasks whereas the physiotherapy group could improve on the simpler dexterity tasks. The majority of patients in both groups showed improved dexterity after exercises, whereby the participants of the VR group typically showed steeper gradients (more improvement) between the pre- and post-exercise tests.

7.4.4. Range of motion

The mean changes in ROM (ΔROM) were calculated between pre- and post- exercise ($\Delta ROM_{Pre\text{-}Post}$) and post-exercise follow-up test ($\Delta ROM_{Post\text{-}FollowUp}$) for all joints and movement directions separately (Figure 32). A positive change reflects an increase in ROM whereas a negative change reflects a reduction in ROM between two test sessions. Between pre-and post-exercise test changes in ROM were minimal in abduction-adduction direction, and the thumb. However, the VR group showed approximately 10° increases in flexion-extension ROM at the MCP and PIP joints of digits 2-5, which is above the clinically significant level of 5° (McGinley et al., 2009). While flexion-extension range of the DIP joint improved as well in the VR group, only

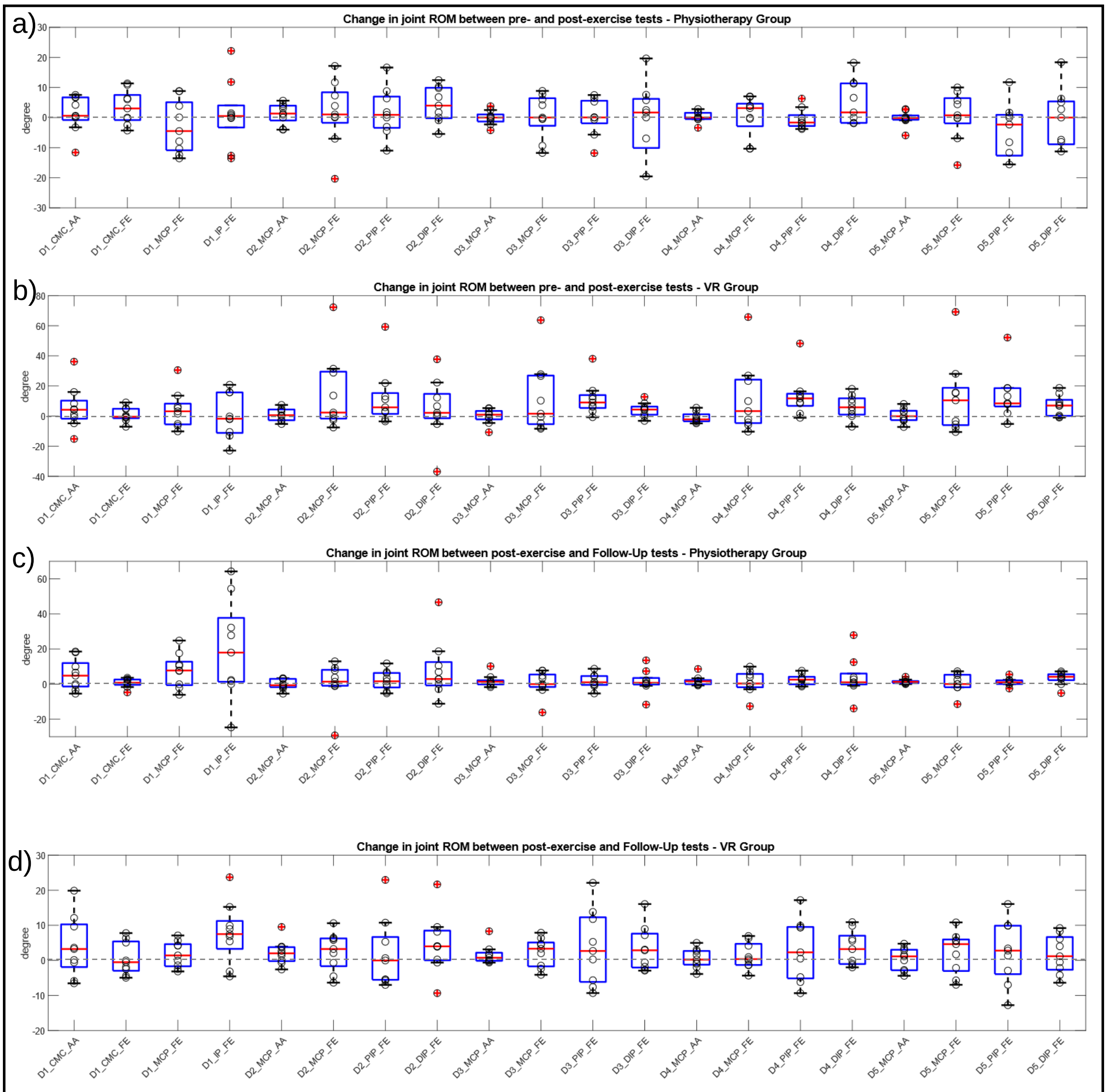


Figure 32: The change in ROM (ΔROM) for 20 ranges (5 abduction-adduction (AA) + 15 flexion-extension (FE) ranges) of digits 1-5 (D1 = Thumb, D2 = Index, D3 = Middle, D4 = Ring, D5 = Little) was calculated between pre-and post-exercise tests as well as post- and follow up tests for the physiotherapy group (a + c) and VR group (b + d). Box-plots show the median ± interquartile range. The whisker length refers to extreme data: if no outlier is present the whiskers extend to the minimum and/or maximum values. In the presence of outliers, the whiskers are equivalent to 1 IQR. Outliers are highlighted in red crosses. The overlaid scatter plot shows participant raw data.

the ROM of digits 4 and 5 improved clinically significantly. The ΔROM in the physiotherapy groups did not change clinically significantly at any joint, with the exception of the middle DIP joint, and little PIP and DIP joints where a clinically significant reduction in ROM was recorded. A Mann-Whitney U test revealed that on average the VR group ($\Delta ROM_{Pre\text{-}Post}$: 5.79°) achieved significantly greater improvements in ROM compared to the physiotherapy group ($\Delta ROM_{Pre\text{-}Post}$: -1.14°) (p = 0.00002).

Between post-exercise and follow-up test both groups showed increases in ROM across most joints. In the VR group all $\Delta ROM_{Post\text{-}FollowUp}$ were clinically non-significant with the exception of the Thumb IP joint flexion-extension range (ΔROM: 7.49°). The physiotherapy group also showed increases in $\Delta ROM_{Post\text{-}FollowUp}$ with the flexion-extension ranges of the Thumb MCP ($\Delta ROM_{Post\text{-}FollowUp}$: 7.46°) and IP ($\Delta ROM_{Post\text{-}FollowUp}$: 17.97°), and the Index DIP ($\Delta ROM_{Post\text{-}FollowUp}$: 6.95°) joints reaching clinical significance. There was no statistically significant difference in $\Delta ROM_{Post\text{-}FollowUp}$ between the groups (p = 0.57).

7.4.5. Qualitative participant feedback

Two qualitative questionnaires were completed: one prior and one after completion of the exercises. Prior to the starting the intervention information regarding the awareness of hand exercises was collected (Figure 33), whereas after the intervention study the participants provided feedback on their respective training programme (Figure 34).

Prior to starting this study 13 participants reported to have engaged in exercises for an average duration of three months. This was for all participants more than three years prior to this intervention study. The participants reported very low levels of motivation to feeling impartial about the exercises, leading to subsequent discontinuation of training. Seven participants reported not to have engaged in hand exercises prior to this study. Out of these seven, five stated that they were not aware of the existence of hand exercises for SSc but would have liked to have received information via their healthcare professionals, whilst the other two did not think hand exercises were necessary for them.

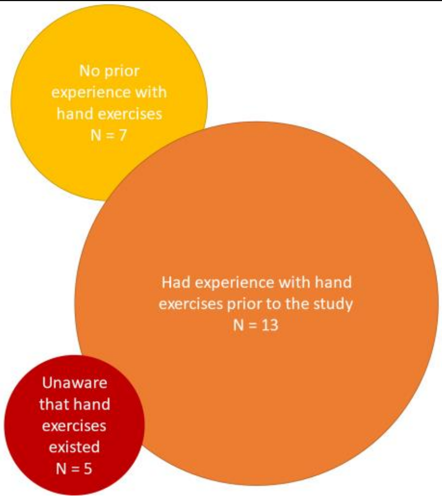


Figure 33: Qualitative patient feedback regarding the awareness of hand exercises prior to study participation of all enrolling study participants (n = 20). A quarter of the participants enrolling in study were unaware of the existence of hand exercises to aid their condition.

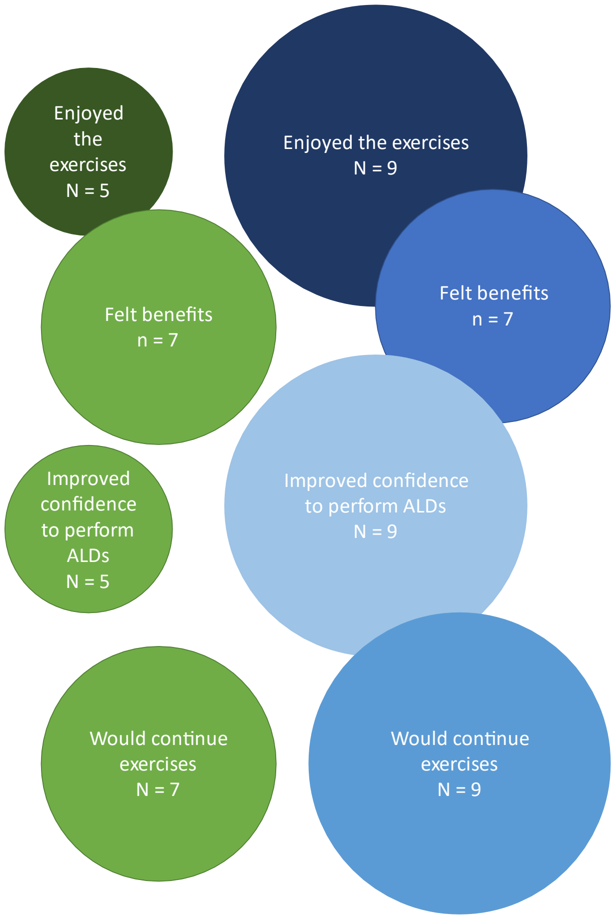


Figure 34: Nine patients completed the physiotherapy programme (green) and Virtual rehabilitation programme (blue) each. Following completion of the respective programme a qualitative approach to evaluate the respective regime was conducted. The VR group showed greater levels of enjoyment and likelihood of adherence to exercises in the future. The perceived benefit was similar in both groups, yet confidence levels increased in all participants of the VR group, but not the physiotherapy group.

After the intervention completion a second questionnaire to evaluate the patient perception of their exercise programme was conducted with the nine participants who completed the study in each group.

Participants of the physiotherapy group showed varied responses. While five stated they enjoyed the exercise programme, the other four disagreed. Similarly, seven participants felt benefits of hand exercises whereas two strongly disagreed. Three participants commented on improved levels of confidence and five stated it made them more aware of their hands and are more willing to attempt ADLs on independently. Seven participants stated that they would continue the exercises because of a potential benefit, whilst two did say they would not adhere past this intervention study. Common barriers acknowledged by the participants was the monotonous exercise structure and time barrier. People reported difficulties to prioritise the exercises over other commitments. Further, most participants in the physiotherapy group did not complete all 12 prescribed exercise sessions, but missed one or two.

The participants of the VR group all enjoyed their training programme and stated they would like to continue the exercises, with two even be willing to invest financial resources to this despite five of them finding the exercises painful at times. Seven stated they felt a benefit, whilst two were uncertain regarding their joint mobility improvements. All reported increased confidence levels after the exercises. All nine participants stated they enjoyed the game setting as they did not realise they were doing exercises in the playful environment (x9), that it was fun (x6) and that it made them competitive against themselves and eager to see improvements in game scores (x4).

7.5. Discussion

Virtual rehabilitation had a greater beneficial response than physiotherapy over the four-week exercise period. On average both groups showed similar decline in hand function after four weeks of no exercises.

The FTP, as a simple clinical measure for finger mobility impairment (Torok et al., 2010), was improved in both groups after four weeks of exercises. Overall, the VR group showed greater improvements after exercises. The magnitude of change in FTP between test sessions is similar to the changes in FTP following an intervention programme of tissue massages and hand stretches (Bongi et al., 2009), who reported a reduction of 0.75 cm following their intervention, which was maintained at follow-up. In comparison the physiotherapy group showed a reduction of 0.5 cm, while the VR group (1.5 cm reduction after exercises) showed greater improvements than both physiotherapy and physiotherapy combined with tissue massages. It is important to note that some patients had an FTP of 0 on the dominant hand despite having overall visible movement impairment. An FTP value of 0 prior to exercises was linked to either asymmetry (i.e. not all fingers touched the palm during maximum voluntary flexion), or the patient could touch the palm with the tip (0 cm distance) but was not able to actually squeeze the fingers into the palm as a healthy individual would. This might explain the insignificant change in FTP between test sessions. This would have especially affected the results of the physiotherapy group where five participants could touch the palm before the intervention compared to the two participants in the VR group.

The CHFS, as a measure of inability to perform ADLs, was reduced in both groups before and after exercises, reflecting an improved ability to perform ADLs. While the physiotherapy group showed a reduction of 11 points on the scale (out of 90), the VR group could only improve by 6 points after the four-week training block. Bongi et al. (2009) studied the effect of combined exercises and tissue massages and found a decrease by 13 points on the CHFS, which is in agreement with the results of the physiotherapy group. The additional two points in reduction reported by Bongi et al. (2009) could be explained by the intensity (daily exercises) and additional tissue massages. Contrary to this, an RCT by Rannou et al. (2017) showed only a reduction by five points after one month of physical therapy, which is closer to the findings of the VR group in this study. The CHFS provided a patient-reported outcome measure about the perceived benefits of exercises on their ADL performance. The reduction in score therefore showed an improvement in ability to perform ADLs, suggesting at least short-term beneficial effects of exercises. The data in this study matches the data presented in the literature, however, as the CHFS relies on patient feedback, the mental health status and attitude towards their disability will affect this measure. This is outlined by psychological models, such as the Kübler-Ross model (Bolden, 2010). A prominent example from this study is one participant of the physiotherapy group, who reported a drop of 61 points after four weeks of exercises, reflecting a transition from very impaired to no impairment, and maintained a level of no impairment at four weeks after exercise completion. This patient further reported feeling more confident, less depressed and conscious about their hands and was exceedingly more confident to complete ADLs independently.

Finger dexterity improved in both groups, but in summary the VR group showed greater improvements than the physiotherapy group. Dexterity has been assessed in some studies as part of the Arthritis Hand Function Tests (Backman et al., 1991), which includes a 9-hole peg test and measures time required to move the pegs. Based on this test, studies have reported improved levels of dexterity following exercises or manual massages (Mancuso and Poole, 2009). The magnitude of change can however not be directly compared to the keyboard tapping speed measured in this study. It has been suggested in the past that there might be a neurological component to the disease (Amaral et al., 2013), which is supported by data in this study, and data reported in the literature, showing improved dexterity following training. Finger dexterity is one contributor to hand function, therefore, dexterity should be targeted in interventions. The data presented in this study is limited as the interventions predominantly targeted the range of motion. Future research should therefore explore the effect of dexterity-specific exercises in patients with SSc to determine the contribution of a deteriorated finger dexterity to reduced hand function.

The ΔROM calculated between test sessions showed very variable results. While the median ΔROM was mostly close to 0°, some clinically significant increases (>5°, (Gajdosik and Bohannon, 1987; McGinley et al., 2009)) in ROM were measured for the FE range. The VR group did show greater improvements on average, however, there were many outliers identified in both groups, which will likely have skewed the analysis. AA ROM was improved in both groups, whereby the VR group showed greater improvements. We identified motion limitations for the AA range in Chapter 4, which led to the integration of an AA range-specific mode in the VR game. The only small AA ΔROM might be due to the smaller AA ROM than FE ROM available in general. Both groups included exercises for AA range, yet, the VR group did show greater improvements than the Physiotherapy group, meaning that the movement in AA can be rehabilitated and should be targeted in exercise regimes.

Participants of the VR group reported higher levels of motivation to continue the exercises as they felt a beneficial effect from the exercises. Participants of the Physiotherapy group had strongly conflicting responses on motivation, and were found to be less likely to continue the exercises in the future, despite reporting improved ability to perform ADLs and feeling more confident about their hands. The low adherences and risk of drop out are therefore consistent with the existing literature.

While the VR group showed greater magnitudes of improvements across the tests in general, it is important to note that the VR group completed supervised exercises, while the physiotherapy group only had three test sessions and a weekly phone call (approximately 10 minutes) in the training phase. This could have potentially discouraged the physiotherapy group as they could see from the provided information sheet that the second group received weekly in-person visits, thus potentially leading the participants of the Physiotherapy group to believe they are at a disadvantage and thus reducing their efforts. Further, the effect of supervision on exercise effectiveness has been reported in the literature and could have led to an inflation of positive results in the VR group due to the Hawthorne effect. Unfortunately, due to technical limitations, it was at this stage not possible to offer the VR group an unsupervised intervention. However, this should be explored in future research. The motion data, collected with the Leap Motion device could not be processed with the neural network approach outlined in Chapter 6 due to inaccuracies in the NNs predictive ability. Therefore, the ROM is subjected to the systematic errors of the LM algorithm. However, as the data was collected under the same conditions and with the same device, the extent of the error is thought to be identical between sessions and for all subjects, which justifies the use of ΔROM as an outcome measure. Due to this limitation, the calculated magnitude of the changed ROM cannot be compared to other literature data.

In general, the patient cohort was very broad in their disease status, which is reflected by large interquartile ranges across all numerical measures. Further the group sizes were small (n=9) after dropout, limiting the ability to make clear clinical suggestions.

7.6. Conclusion

Both intervention groups showed improvements for ability to perform ADLs, finger mobility, as well as dexterity. Across all measured variables the VR group showed greater improvements on the median values. The individual participant improvement was greater in the VR group as well for the FTP, CHFS and finger dexterity tasks. Non-significance of results can be due to large interquartile ranges which are likely due to the broad patient cohort considered in this study. Patients reported positive feedback regarding motivational levels in the VR group, while the physiotherapy group showed less indication for future adherence to their programme. This pilot study has shown that VR has the potential to improve hand function and overcome adherence barriers compared to physiotherapy. Whilst proof of concept was successful, a multi-centre randomised control trial with long-term follow-up and more participants of various stages is required.

Chapter 8: General discussion

Thesis structure				
Chapter	Title	Structural design	Addressed Aims	Linking to Chapters….
1	Introduction to the research			
2	Literature review	Literature review		3, 4, 5, 6 ,7
3	Describing the development of an opto-electronic and a markerless motion capture approach for the hand and subsequent kinematic modelling	Developmental study: Technical chapter outlining the design of kinematic models used in this thesis		4, 6 and 7
4	A comparison of hand movements during functional tasks in patients with systemic sclerosis and age - and hand dominance-matched healthy controls	Experimental study: Comparing hand movements of patients with SSc to age-matched healthy controls to quantify joint specific movement impairments	**Aim I:** Accurately assess the hand movement limitations of patients with SSc during functional tasks using three-dimensional motion analysis	5 and 7
5	Method chapter: Design of a virtual rehabilitation game for systemic sclerosis informed by three-dimensional movement analysis	Developmental study: Technical chapter with a detailed description of the design of a virtual rehabilitation tool for patients with SSc	**Aim III:** Deploy the portable motion capture method into a virtual rehabilitation context	7
6	Improving the accuracy of the Leap Motion controller for purposes of markerless hand motion capture using artificial neural networks	Experimental study: Assessment of the Leap Motion controller to accurately measure hand kinematics before and after the application of neural networks in comparison to an opto-electronic measurement approach.	**Aim II:** Develop a portable method to capture 3D movement	7
7	Virtual Rehabilitation vs. Physiotherapy: A comparison of two rehabilitation approached on hand function in patients with systemic sclerosis	Experimental study: RCT comparing the effect of two intervention programmes to improve hand function in patients with SSc	**Aim IV:** Examine the effect of the virtual rehabilitation tool in comparison to traditional physiotherapy on hand movement limitations	3, 4, 5, 6
8	General discussion			

8.1. Overview

The main aim of this research was to investigate the effect of a purpose build, portable virtual rehabilitation (VR) tool, informed by an objective 3D mobility assessment of hand function in patients with SSc. Hand function combines aspects of mobility, dexterity and strength, and when impaired, affects ability to perform ADLs. A reduced ability to perform ADLs has negative impacts on mental health, independence and quality of life (Maddali-Bongi et al., 2014; Nguyen et al., 2014). In the first study, movement deviations from normality were assessed during functional tasks leading to the identification of movement impairments at all joints in both flexion-extension and abduction-adduction directions. This information was then used to inform a novel VR exercise tool to train finger mobility in a multi-joint approach. In a pilot study, the effect of training on the VR tool was compared to the effectiveness of conventional physiotherapy. The training programmes exposed the participants of both groups to exercises targeting the range of motion, however, finger dexterity was also assessed as dexterity is an aspect of hand function. A secondary aim was to create a portable device for hand motion analysis. Using the LM and artificial neural networks, a study on healthy controls was conducted to predict accurate kinematic data from a commercially available sensor. While this project showed promising results in healthy controls, several flaws in the prediction were identified. In order to use the method for future research in both healthy and pathologic populations, the current limitations and flaws need to be resolved.

While some of the results were already discussed in the prior chapters, general questions need to be addressed under the consideration of the combined chapter results. The following questions will be addressed over the next sections:

- Do objective measures provide new, valuable information for hand function in SSc relevant to clinical practice?

- Should ability to perform activities of daily living be used as a primary outcome measure?
- Can a portable VR tool alone realistically increase adherence to exercise?
- Can non-specialised commercially available sensors, such as the Leap Motion controller, be a good alternative to gold-standard opto-electronic systems?

8.1.1. Do objective measures provide new, valuable information for hand function in SSc relevant to clinical practice?

The functional tasks assessed in Study 1, opening a zipper or a lid, are frequently reported as problematic by patients with SSc. Therefore, it might be no surprise that it was identified that patients struggled more than the age-matched healthy controls. In a second step the contribution of individual joints to the overall MDP_{mean} was assessed by eliminating one joint at a time from the MDP calculation. The existing literature states that the flexion range of the interphalangeal (IP) joints is predominantly affected. We found contrasting information where all joints and degrees of freedom are equally impaired. Further, our data indicated that extension range is impaired prior to flexion, suggesting that the currently used FTP as an assessment for finger mobility is insufficient and needs to be enhanced by a finger extension test and a finger spread test, especially in early stages of the disease.

The translation of the MDP into clinical practice as an objective measure faces several barriers, such as cost, expertise and time demand. While all these barriers could be overcome with a portable motion capture system, such as the Leap Motion controller in association with artificial neural networks, the use and acceptance of the MDP approach by clinicians is a different challenge which can only be overcome with persistence and quality research conducted.

Until the barriers may be solved, the MDP can be replaced by simple measures that evaluate more than one movement. Therefore, it was suggested to include a finger spread-test and a positive prayer sign test during routine appointments. These take up very little time and provide simple distance measures, which are easy to understand by healthcare professionals. The MDP, on the other hand, is more complex to understand and could possibly best be used to measure disease progression over time.

While the level of detail offered by the MDP might not be informative to the patient or directly affecting patient care, it provides information which can be used to design research studies. The design of any clinical research study needs to be justified by scientific or medical literature. When searching the literature there are multiple ways to identify a research questions, for example by identifying a gap or conflicting evidence. Research may also be justified if methodologies or the approach to research was flawed or prone to bias. Justifying a potentially very expensive drug or physical exercise intervention study purely based on subjective patient-reported outcome measures (PROMs) could therefore be considered a mistake, and potentially lead to reduced funding. In order to develop rigorous study design objective measures are essential to assess effectiveness without subjective bias. Therefore, the MDP and MDP_{mean} as presented in this thesis provide new information, which can be used for the design of intervention studies and also to examine the effectiveness thereof.

8.1.2. Should ability to perform activities of daily living be used as a primary outcome measure?

A virtual rehabilitation (VR) tool was designed based on the information of the joint specific MDP_{mean}. This novel tool could train finger extension-flexion range as well as abduction-adduction range in a playful environment that matched the individual's ability. After four weeks of intensive exercises (3 x 30 min a week) finger dexterity and mobility had improved significantly. The ability to perform ADLs was also increased, however not significantly. In comparison to conventional physiotherapy virtual rehabilitation performed slightly better when considering median values, but not significantly. Further the magnitude of change in patient-reported outcome measures (PROMs) was not correlated to the results of objective assessments.

Based on these findings, it is debatable if PROMs should be used as a primary outcome measure to assess effectiveness of exercises or to assess mobility in clinical practice. PROMs are used to evaluate if a clinician's treatment has the intended effect or if changes are required. Therefore, in research PROMs are a useful tool to evaluate the patient perspective on the process and identify means to improve the research process or identify new areas of research. The use of PROMs is considered central to good clinical practice and integral to patient-centred care (Kingsley and Patel, 2017). However, PROMs are known to be influenced by psychosocial factors, such as gender, age, ethnical background, level of education, disease activity at time of the evaluation and marital status (Frost et al., 2007). Further, if used in context of evaluating a new treatment, the type of intervention, and purpose (curative or pallative), are likely to influence responses to repeated PROMs over time (Frost et al., 2007). Further, depression, anxiety and social isolation are commonly reported for patients with SSc (Amaral et al., 2013; Cinar et al., 2012; Del Rosso et al., 2013; Nguyen et al., 2014). One example regarding the potential effect of psychology on PROMs is shown by a patient of the physiotherapy training group in the intervention study (Chapter 7), who showed a drop of 61 points on the CHFS (from severely impaired to no impairment at all), but only very minor positive changes on the objective measures. This patient further reported to be very depressed prior to starting the exercises, whereas depression was not a factor after four weeks. At the same time, patients stating no depression or anxiety prior to exercises still improved their ability to perform ADLs. Therefore, in order to fully understand and standardise responses to PROMs, a psychological assessment component is required. This could be achieved by adding more questionnaires and scales specifically designed to assess depression and anxiety in patients with uncurable diseases, such has the Hospital Anxiety and Depression Scale (Snaith, 2003) or the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). The Canadian Occupational Performance Measure (COPM) (Law et al., 1991) is a tool to evaluate occupational performance in multiple areas of life over time under consideration of special circumstances. It can be predominantly used to track changes over time taking into consideration tasks that are not specifically linked to the hands but that affect overall health and well-being.

Psychological evaluation is very important in chronic conditions, as patients have to live with an uncurable disease which will eventually lead to early death. Access to a skilled psychologist to talk about and learning to cope with such a severe diagnosis would be invaluable (Frost et al., 2007). Patients with SSc have annual or bi-annual check ins with their care clinician, which includes multiple other tests regarding the physiological capacity, such as echo cardiograms, lung capacity tests and blood tests as well as a series of PROMs. A psychological assessment does currently not form part of this routine care, however, in order to fully understand PROMs and also some physiological tests, a psychological evaluation is required.

8.1.3. Can a portable VR tool alone realistically increase adherence to exercise?

One of the reasons to use VR was to counteract low adherence rates which are reported in the literature in relation to conventional therapy. The VR literature does indicate higher motivational levels towards VR than other therapies. The patients in the intervention study presented in this thesis (Chapter 7) filled in a non-validated questionnaire to evaluate likelihood of future adherence and motivation. Motivation is a complex term, which refers to needs, desires, wants or drives of a person towards an ambition or goal (Souders, 2019). Motivation has also been linked to adherence for exercises in a sporting and therapeutic context. However, it depends on the motive itself that drives the ambition how well someone will adhere to exercises. Ryan et al. (2018) found that motives focussing on enjoyment, competence and social interaction will increase adherence to sporting exercise. Appearance and fitness as primary motives were less linked with adherence. The effect of motive on adherence could potentially be similar for rehabilitation programmes.

While VR is likely to improve the motivational aspect by providing a playful and potentially competitive environment, there are several other barriers that influence adherence. Most frequently reported is a time burden, or difficulty to prioritise exercises over other commitments. Further, completing therapeutic exercises can be isolating as family and friends might not share or understand the need for the exercises. In a sporting environment this barrier could be overcome by joining group exercise classes or a sports team. In rehabilitation this is more difficult. A potential solution could be to provide VR tools as an online game where patients can compete or chat to one another. Integrating a social aspect to improve adherence goes well beyond the scope of this thesis.

Work presented in this thesis also indicated a lack of educational resources, with five patients having been unaware of hand exercises for systemic sclerosis. Education of patients in regards to potential self-managed rehabilitation exercises is the first step which needs to be addressed by healthcare professionals. Patients need to be encouraged to complete exercises and be provided with resources which highlight not only what exercises to do but also illustrate beneficial effects of exercises to give the patients a purpose. Patients, who participated in the intervention study (Chapter 7), continued to complete exercises after the research study as they felt a benefit after having been provided with resources, materials and guidance. Unfortunately, the literature states low number of referrals to professionals and educational resources to be handed out in clinics (Bassel et al., 2012). If educational resources are not in place, no intervention, even a portable and enjoyable game, can possibly improve adherence, as a game alone cannot convey the importance or purpose of exercises. Goal-setting is an important factor for any kind of exercises, and especially supervised goal setting to agree on realistic goals has been associated with more frequent achievements of these goals (Coppack et al., 2012; Nelis et al., 2018; Wilson et al., 2020). A supervised counselling session with an experienced health care professional to set realistic goals and manage expectations prior to an exercise prescription in form of virtual rehabilitation or physiotherapy could greatly benefit adherence to exercise programmes in patients with systemic sclerosis.

8.1.4. Can non-specialised commercially available sensors, such as the Leap Motion controller, be a good alternative to gold-standard opto-electronic systems?

Research in this thesis relied on two main methods: a marker-based and a markerless motion capture approach. Both methods have benefits and limitations discussed in the previous chapters (Chapter 2 and 3). In an attempt to overcome the limitations of both systems, an artificial neural network was applied to generate accurate motion data from a cheap and portable device, in this case the Leap Motion controller (LM). This protocol was tested in young healthy adults and showed on average a reduction in root mean square error. While the reductions were significant, the agreement between NN prediction and gold-standard measurements of kinematics was not perfect, and rather inconsistent. The hand has 29 degrees of freedom, resulting in several million theoretical ways to move our hands. Given the sheer amount of possible movements and the many mathematical assumptions made in the kinematic models prior to neural network analysis, it is not necessarily possible to achieve perfect agreement between the two motion capture techniques and resulting models.

Hand motion analysis is unlikely to be done in healthy controls, but rather in impaired individuals. The impairment could be linked to neurological conditions, such as stroke or Parkinson’s disease, or it could be due to deformities, such as in SSc or rheumatoid arthritis. Structural impairments visible to the eye cannot be detected by the LM and the NN could not correct for the impairments either as it was not configured to do so in the first place. In Chapter 4 it was concluded that all joints are impaired, but the large spread of data also indicated that movement impairments very variable between patients, although some patterns could be identified. The large variability of impairments in turn will increase the difficulty of a NN to predict data from the low-quality input source. To overcome this barrier a sizeable amount of data from patients with various degrees of impairment is required. Given the rarity of the disease, this will involve a larger multi-centre study to obtain the desired sample size.

8.2. Limitations

8.2.1. Sample size

As SSc is a rare disease, identifying suitable participants can be challenging. Our studies included 10 patients for a cross-sectional evaluation of hand function, and 20 (split into 2 x 10 patients) for an intervention protocol. These numbers are quite small, even in comparison to other non-pharmacologic studies in SSc evaluating non-supervised and remotely monitored interventions (Mugii et al., 2006; Poole et al., 2013c; Rannou et al., 2016; Rannou et al., 2017; Willems et al., 2015b). However, if interventions are required to be supervised, such as the VR group in this research, the cohort sizes are smaller (Bongi et al., 2009; Bongi et al., 2011; Piga et al., 2014; Pils et al., 1991; Sandqvist et al., 2004a; Uhlemann et al., 1990; Werner and Eder, 1996). Therefore, based on protocol design the patient cohort size is consistent with other studies in the literature. Nevertheless, the small sample size diminished the ability to generalise the findings from this study and an evaluation of the tested protocols in a larger, scientifically justified sample size is required. The data presented in this thesis could be considered a pilot study, which allowed the calculation of sample sizes. It was determined, that 80 (based on the FTP data), 115 (for ROM assessments) and 490 (CHFS) patients are required to complete the protocol in order to obtain values which reflect the whole population, thus justifying the demand for a larger cohort study. These calculations were based on the standard deviations and 95% confidence interval of the data.

8.2.2. Variability of patient cohort

The patient-centred studies include not only a small sample size, but also a highly variable cohort. The disease does not have a clear progression pattern, and the used inclusion and exclusion criteria were insufficient to produce a narrow cohort. This is particularly apparent in the intervention study, where we identified large interquartile ranges and multiple outliers across all measurements. To overcome this in the statistical analysis, non-parametric data testing was applied, however, the cohort effect (McAdams, 2008) is likely to influence the results. Therefore, all results from patient data merely described a general trend which needs to be interpreted with caution. To generate a more focussed patient group, some inclusion and exclusion criteria should be amended. The patients had a large range of movement impairments, which could have been prevented by adding to the inclusion criteria an FTP of 1-6 cm or similar, to ensure that patients have at least some visible impairment prior to the intervention programme. Further, a criterion for mental health should be added to the exclusion criteria, to minimise the effect of psychological factors on movement ability.

8.2.3. The black box that is the LM integrated algorithm

The LM is a commercially available sensor for touchless interaction with computers. The LM hosts an inaccessible extrapolation algorithm to reconstruct a 3D hand skeleton based on two video images. Due to the inaccessible nature of the algorithm, the understanding of the generation of the skeleton is limited. Yet, we can tell from the visual image of the skeleton that the fingers are never entirely straight with the LM algorithm. Further, pathological deformities are unlikely to be picked up by the LM if only a single joint is affected. For example, a long-standing fixed flexion contracture of a specific joint in an SSc patient would not be correctly identified. The application of the neural network could potentially offset this error if the NN is trained with sufficient patient data. Yet this was not done in this study. Instead we calculated changes in the possibly incorrectly measured ROM to evaluate the magnitude of change before and after exercises. While the ROM measures themselves are likely inaccurate if they were to be compared to goniometer data or motion capture data, the error induced by the LM does not change over time. Therefore, the pre- and post-exercise measurements are affected by the same error, making the magnitude of change between test sessions a relevant measure. Yet, the absolute values should not be compared to goniometer or motion capture data (Coton et al., 2016; Nizamis et al., 2018).

8.2.4. Supervised and non-supervised exercises

In the intervention study we compared a supervised VR group to a mostly non-supervised physiotherapy group. This was justified as there is already evidence that physiotherapy can be used to rehabilitate hand function in non-supervised studies (Piga et al., 2014; Poole et al., 2013c; Rannou et al., 2017). For the VR group there is no data in the literature and this study's purpose was to identify if VR is a suitable tool for hand function rehabilitation in patients with SSc. Further, funding for the cost of equipment (laptops, LM controllers and D-Flow software licenses) that would be required to conduct the VR group as a non-supervised group was not available. However, comparing supervised and non-supervised groups is frequently discussed in the literature for intervention studies ranging from children, to adults and from healthy to impaired cohorts (Coll-Fernandez et al., 2016; Florez-Garcia et al., 2017; Hartvigsen et al., 2010; Nicolai et al., 2009; Rustaden et al., 2017). The Hawthorne effect refers to the awareness of being observed and the subsequent possible impact of behaviour on the results while enrolled in a research study (McCambridge et al., 2014). Based on the theory of the Hawthorne effect, the results of the VR group could have been inflated. Simultaneously the non-supervised physiotherapy group could have felt disadvantaged compared to the supervised VR group therefore reducing the effort put into training. Controversially it could be argued that participants in the physiotherapy group would increase the effort to compensate for the lack of supervision. To minimise the possible Hawthorne effect, verbal engagement was kept to a minimum during the VR training sessions. The research team also supervised the first physiotherapy training session. After the first training, the participants of the physiotherapy group received weekly phone calls to provide some interaction between the researcher and the patient.

8.3. Recommendations for future research

Hand movements are complex, and therefore the MDP provides an interesting measure (Chapter 4). While the MDP is validated in the lower limb, it has not yet been compared to other potential indices in the hand. The MDP_{mean} can be used to monitor disease progression, of which little is known about in SSc. It is currently unknown how sensitive the MDP_{mean} is regarding the development of flexion contractures.

The use of artificial neural networks to improve the accuracy of the LM showed very promising results, but the error between LM and Vicon was never completely diminished (Chapter 6). Future research should primarily aim to enhance and improve the current methods and data sets. The data sets should be enhanced with additional data for all movements from participants of multiple ages. The processing of data prior to NN training has major impact on the quality of the NN. In this study we offset a single joint to the same position to overcome the difference between two distinct Cartesian coordinate systems. A more accurate approach would be the merging of the two systems using ‘Iterative closest point’ (ICP) methods (He et al., 2017). ICP refers to an algorithm designed to minimise the difference between two data clouds, such as 3D motion data. A PCA and z-score were performed to reduce dimensionality and scale the data. Both the PCA and z-score had to be performed on an accumulated matrix in order to be able to reverse the processes after NN training. For a 10-fold cross-validation a PCA and z-score could have been completed on individual trials, which would have improved the data. However, if tested with new subject LM data only (Vicon data not present) the PCA would not be reversible to predict data as the principal component coefficients and mean of the corresponding Vicon data are essential. Therefore, a method to overcome these processing barriers needs to be identified. The NN was trained with joint centre data. For a more direct approach angle data could also be used to train the NN. In this research study a shallow neural network was trained. Given the complex temporal-spatial data, a time-series or deep neural network could improve the NN prediction. Once corrected for healthy individuals, the NN approach needs to be trained with movement data of impaired participants. The LM could potentially be insensitive to pathologic hand deformities and impairments, and thus the NN predictions could be inaccurate for patients.

Once the Leap Motion method has been improved, this system should be integrated into a virtual rehabilitation programme. While the current tool can be played without accurate angular kinematics (Chapter 5), more advanced tools could use kinematics from a real-time neural network to either drive the game or as another form of bio-feedback to show progress of hand mobility in response to exercises. The greatest challenge would be the translation of the improved methods to a large-cohort multi-centre randomised controlled trial.

Data in this thesis (Chapter 7) indicated positive short-term effects of VR for hand mobility in patients with SSc. However, these measurements are subject to limitations, among which is the small sample size, supervision and short exercise period. The study fulfilled the purpose of a pilot study into the initial effects of VR in SSc, and should in a next step be enhanced to non-supervised VR in a large sample size with a long follow-up period (at least 12 months). It is thought that VR improves adherence at this stage but this needs to be verified by extensive follow-ups. Further a tele-monitored approach could be employed in an attempt to compromise between supervised and non-supervised exercises. If a larger study is conducted, psychological expertise should be drawn upon to evaluate the psychological influence on the performance of exercises, adherence and the effect of exercises on the mental health, confidence and self-efficacy.

8.4. General conclusions

Despite hand movement impairments in patients with SSc being evident and appreciated by clinicians, there is not much objective data regarding the magnitude of impairment in the literature. Most studies evaluated the impact of the impairments on the quality of life and ability to perform ADLs using self-reporting questionnaires. Other studies report subjectively observed data. In this thesis movement deviations from healthy controls were objectively assessed and identified that movement impairment is evident at all joints and in all movement directions, contrasting the literature stating that predominantly the flexion-extension range of the interphalangeal joints is impaired. This new knowledge was then incorporated into a purpose built, portable virtual rehabilitation game to train the impaired movements identified. The novel intervention tool was then tested in comparison to conventional physiotherapy. After four weeks of intensive exercises patients showed improved finger mobility, finger dexterity and ability to perform ADLs in both groups, while the VR group showed greater improvements. To the author's knowledge, this represents the first study on VR in patients with SSc.

The initial studies were conducted in a conventional lab-based environment, however, to be able to generate translatable research the stationary, gold-standard approach needs to be complemented with low cost, lower accuracy but more feasible, portable motion capture methods, such as the Leap Motion controller. Advanced mathematical algorithms like ANNs could reduce the error of the LM relative to gold-standard Vicon data, however, the inconsistency in NN output prevented the application of this method to research at this stage.

The low participant numbers in all studies present a limitation, and a larger sample size would be desirable to meet average cohort sizes of the existing literature. Despite some weaknesses of the research study, the individual patient responses to the exercises have established important insight into the suitability of VR to hand mobility, finger dexterity and ability to perform ADLs in patients with SSc.

In conclusion, hand impairments affect all joints in all movement directions and virtual rehabilitation provides a good option to maintain hand function, including movement ability and finger dexterity, in patients with systemic sclerosis.

8.5. Original contributions to knowledge

Every study presented in this chapter creates new knowledge in the field of Systemic sclerosis and biomechanics.

Study 1 (Chapter 4) saw the application of the Movement Deviation Profile to the upper extremity. To the author's knowledge this is the first time that a movement index has been applied to the upper extremity. The upper extremity, in particular the hand, represents a smaller field of biomechanical research, yet the importance is not to be neglected. An index to show at which time point patients struggle in dynamic tasks is important to not only quantify the level of impairment but also to inform rehabilitation exercises and other interventions.

The concept of virtual rehabilitation is well known, however, a game to dynamically train all finger joints and multiple directions of movement for patients with systemic sclerosis did not exist prior to the research presented in this research (Chapter 5). In fact, even for more common conditions, such as Rheumatoid Arthritis, a game to train hand function is not available, and may benefit from the results of this project.

Markerless motion capture is becoming increasingly more common, however, like every other aspect of biomechanics, the markerless approaches focus on the lower extremity. The Leap Motion might be commercially available, but by using artificial neural networks, the Leap Motion accuracy was improved, thus showing important, and new work to create a hand specific markerless motion capture tool. This work has further won multiple awards at conferences, showing the appreciation of technical detail by the scientific community.

The intervention study was the first study in SSc to assess if virtual rehabilitation has beneficial effects on hand function. Interestingly, similar to the computer game itself, there is currently no other study evaluating the effect of virtual rehabilitation in any rheumatic condition, even the more common Rheumatoid arthritis and Lupus. Therefore, this study contributes important knowledge to the future of rehabilitation exercises, virtually and non-virtually, in rheumatoid conditions.

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Appendices

Appendix 1:

The script below was applied in D-Flow to initiate jumping and falling of the ball in the presence or absence of movement respectively. The script was written in Lua, the integrated coding language for D-Flow, in the Script module.

The script relied on a single input (ratio) which reflected the position of the finger within the range, and created a single output (s) which reflected the displacement of the ball.

Script:

```
if v==nil then
        v=0
        s=0
        ratio_old=0
end
```

At the start, the ball was at it the set start position thus velocity (v) and displacement (s) were 0 and the finger was maximally flexed/abducted this ratio was also 0.

```
g=9.81*inputs.get("g_mult")
```

The fall acceleration of the ball was defined at 9.81 multiplied by the gravity multiplier as defined in the parameter settings in the console.

```
v=v-g*framedelta()
```

The velocity of the ball increased for every frame recorded. The rate of change of the velocity depends on 'g' as defined in the previous step.

```
s=s+v*framedelta()
```

The displacement, thus position of the ball was then defined as the sum of the position of the ball in the previous frame and the product of the velocity of the current frame.

```
ratio= inputs.get ("ratio")
```

Here the ratio, effectively finger position within the calibrated range was added.

```
jump_speed= inputs.get("jump_speed")
```

This line linked the script to the adjustable parameter 'jump speed' which could be manipulated in the console to match player ability.

```
if (ratio>0.8 and ratio_old<0.8) then
```

The conditions of the jumping of the ball were defined as: the ratio has to exceed 0.8 in the current frame and had to be less than 0.8 in the previous frame. This ensured that the ball would only jump once and the player had to flex the finger, followed by another extension (or abduction followed by an adduction respectively) to initiate another jump of the ball.

```
v=jump_speed
```

If the conditions where met, the velocity was changed to jump speed resulting in a single upwards bounce of the ball.

```
end
```

```
if s<-4 then
	v=-v*0.9
end
```

If the ball fell to the ground (displacement -4 from starting position) the velocity of the ball changed and was reduced, resulting in a bouncing ball that, in the absence of movement would become static.

```
if s>2-0.25 then
	v=0
end
```

The position of the ball was calculated from the centre of the ball therefore the ball radius was subtracted to ensure the bouncing would occur at the time the lower margin of the ball touched the ground.

```
ratio_old= ratio
```

At the end of the scrip the ratio of the current frame was stored as ratio_old to be used in the analysis of the next frame

```
outputs.set("Position", s)
```

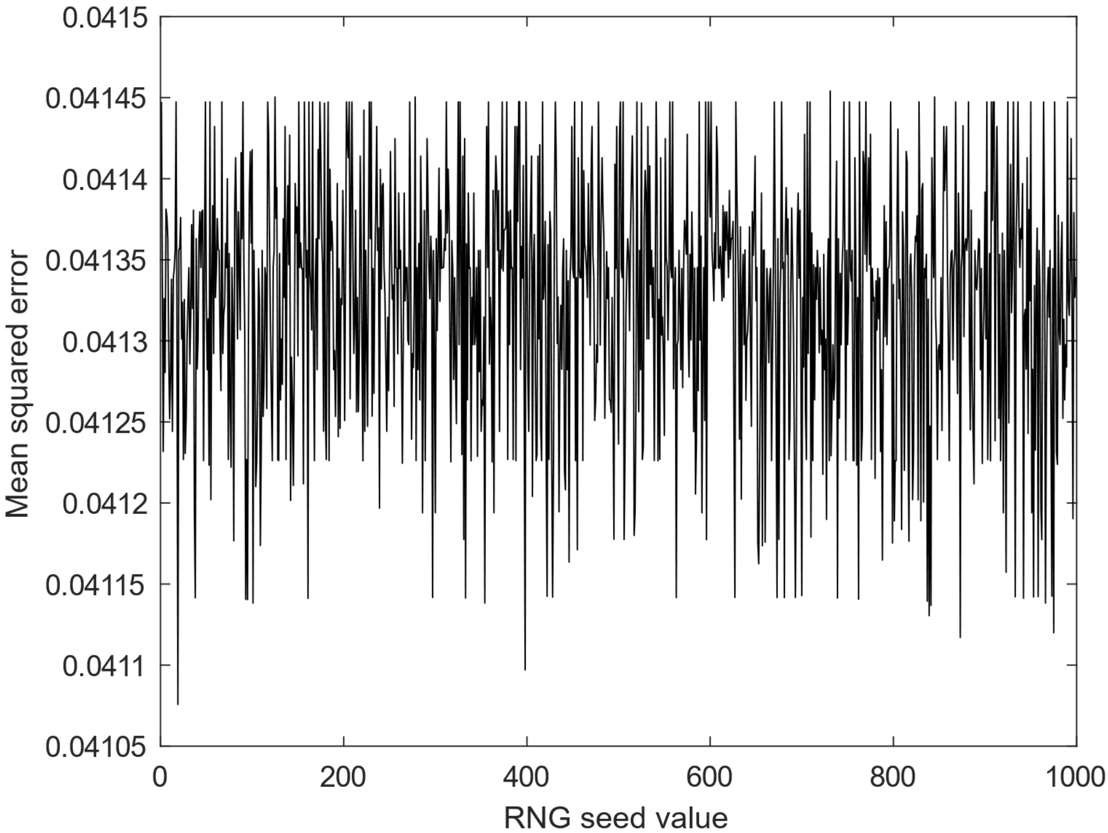
The Position of the ball was generated as output and used further in other modules to drive the game.

Appendix 2:

The random number generator seeds a random number upon creation of any neural network in Matlab. The generated number sets the weights and biases for all neurons in the network, and therefore can affect the predictive strength of a neural network. As the random number is seeded newly each time the network is generated, no NN will ever be completely identical if initiated twice or more times, without constraints on the random number generator.

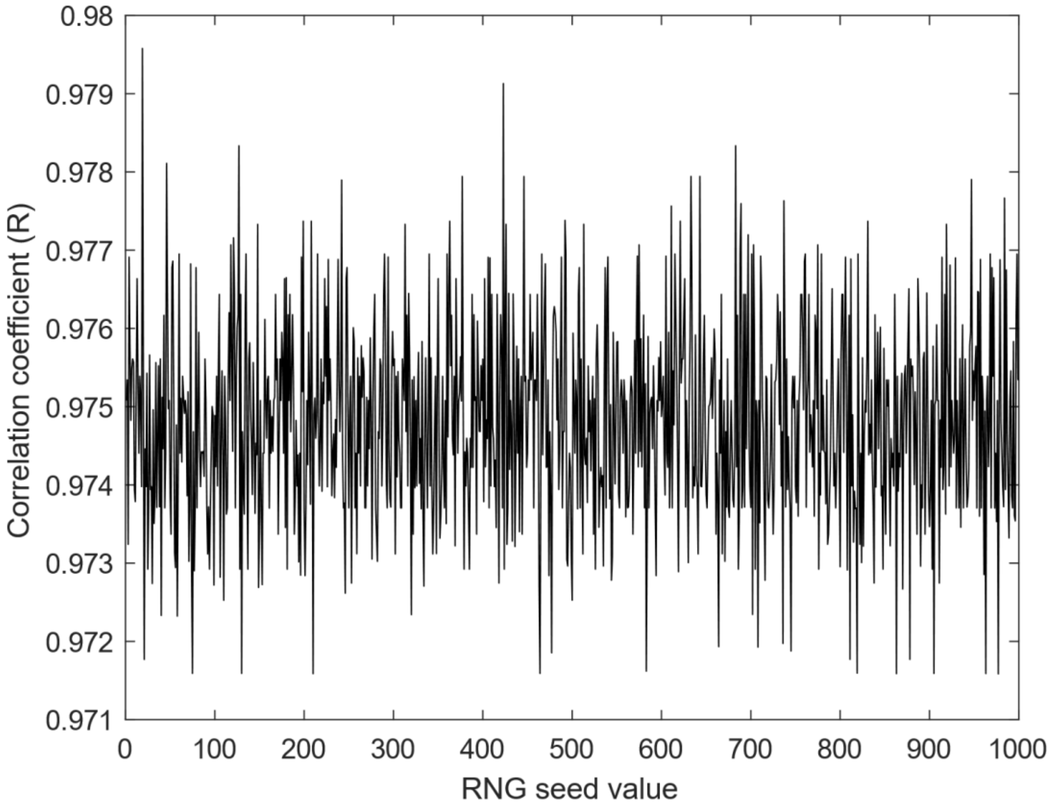
As the random number selected can influence the quality of the NN, the NN was evaluated 1000 times, with the random number generator being controlled. The weights increased from 1 to 1000 in single number increments. The performance was analysed based on the neural network test performance measure (distance between target and output data, measured using mean squared error (MSE)) and the resulting correlation coefficient. The value showing the best performance values, thus smallest mean squared error, and highest correlation coefficients was determined to produce the best result for our data set, in this case 19 as can be seen in the figures below.

The network performance:



The mean squared error was smallest for when the RNG was 19 (MSE: 0.04107), however, the range of MSE over all 1000 seeds was negligible: The average MSE was 0.04132, with the range being 0.00038 MSE (Min: RNG_{19} = 0.04107, Max: RNG_{731} = 0.04145).

The correlation coefficient



The correlation coefficient was highest for when the RNG was 19 (MSE: 0.97913), however, the range of MSE over all 1000 seeds was small: The average correlation coefficient was 0.97481, with the range being 0.00755 (Min: RNG_{464} = 0.97158, Max: RNG_{423} = 0.97913).

Summary

On the sixth significant figure the RNG seed 423 resulted in a higher correlation coefficient than 19. Under consideration of both MSE and correlation coefficient the seed 19 was determined to be the most beneficial. Neither performance, nor correlation coefficient were much affected by the RNG seed, as evident by the small ranges of (<0.01) for both parameters.

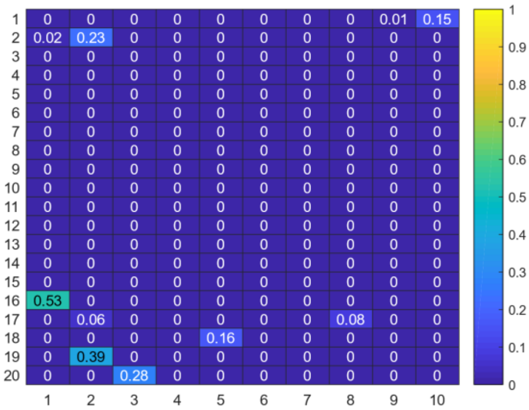
Appendix 3:

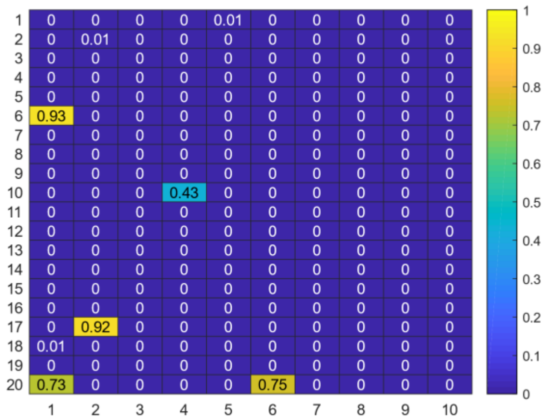
Application of an artificial neural network to predict joint centres and subsequently angles of finger joints during flexion extension movement

Following the same protocol as outlined in chapter 6, a task specific neural network for the left and right hand was generated, trained and tested. The results were assessed using the same methods as outlined in Chapter 6 but the hands were trained and evaluated separately.

Left hand:

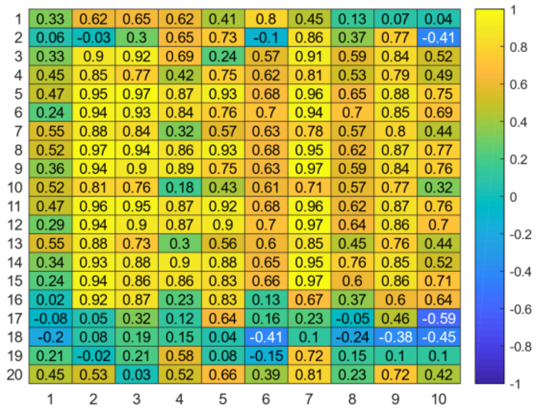
p-value:

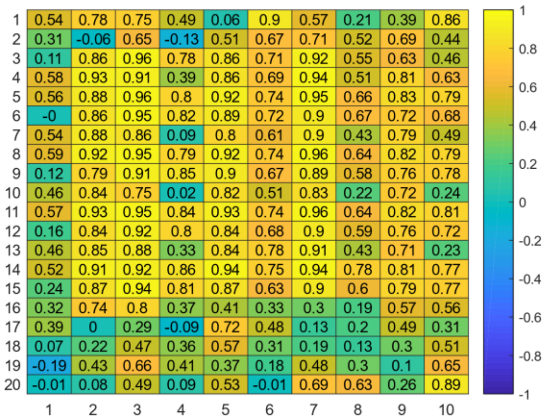




On the left, the p-value for the input (LM) and target (Vicon) correlation is shown. On the right the p-value for the NN output-target correlation. Both LM and NN generated data is significantly correlated to the Vicon target data for most angles (y-axis) and NNs (NN1 - NN10: x-axis). While the output data shows in sum more significant correlations, there are more highly insignificant correlations for the output data as well. These are mostly linked to abduction-adduction angles (row 16-20), which are only minorly moved in the flexion-extension movement the participants followed.

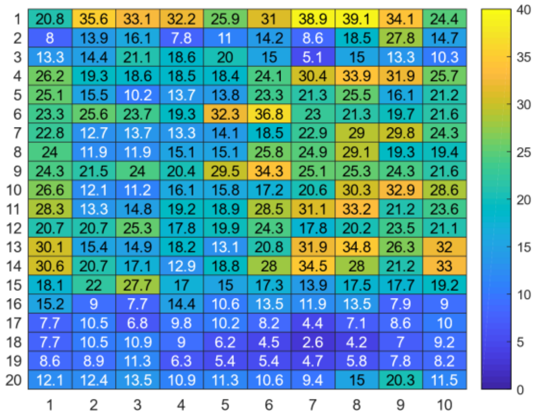
Correlation coefficient (R^2):

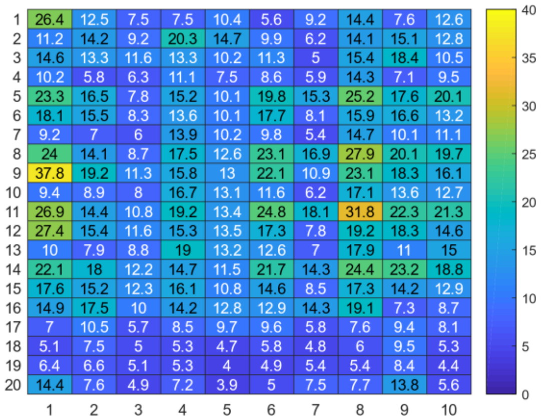




On the left, the correlation coefficient for the input (LM) and target (Vicon) data is shown (mean R value: 0.57). On the right the correlation coefficient for the NN output-target correlation (mean R value: 0.6). In sum, both methods show similar strength of correlation. The abduction-adduction angles (row 16-20) show weak correlations in for both the LM-Vicon correlation and the NN-Vicon correlation, supporting the findings of the p-value table.

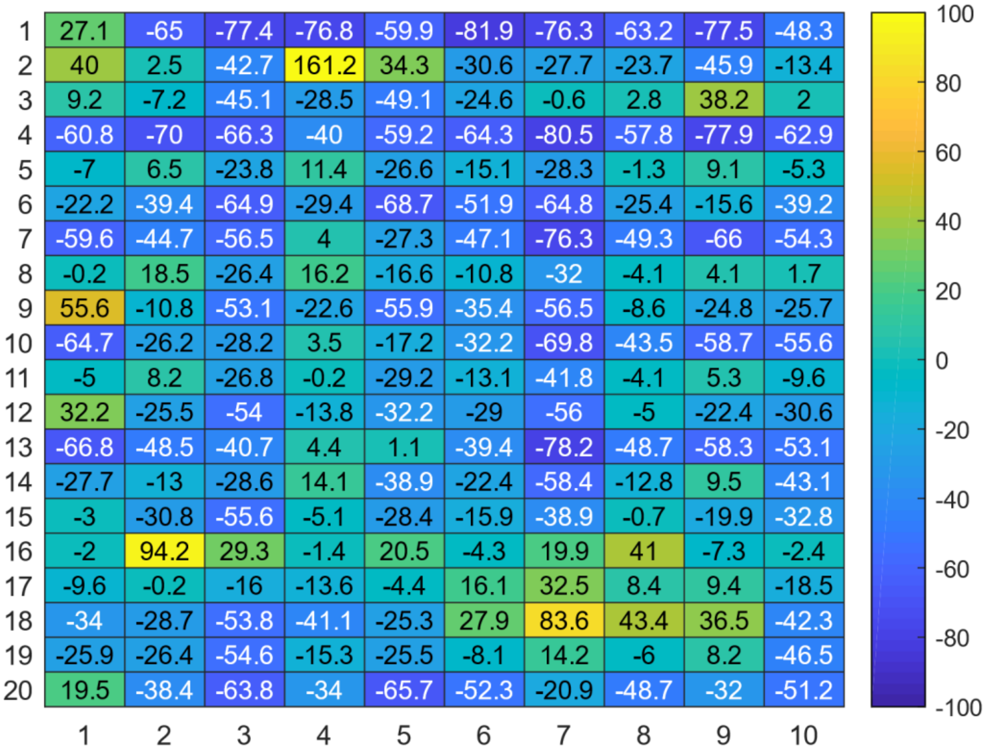
RMSE





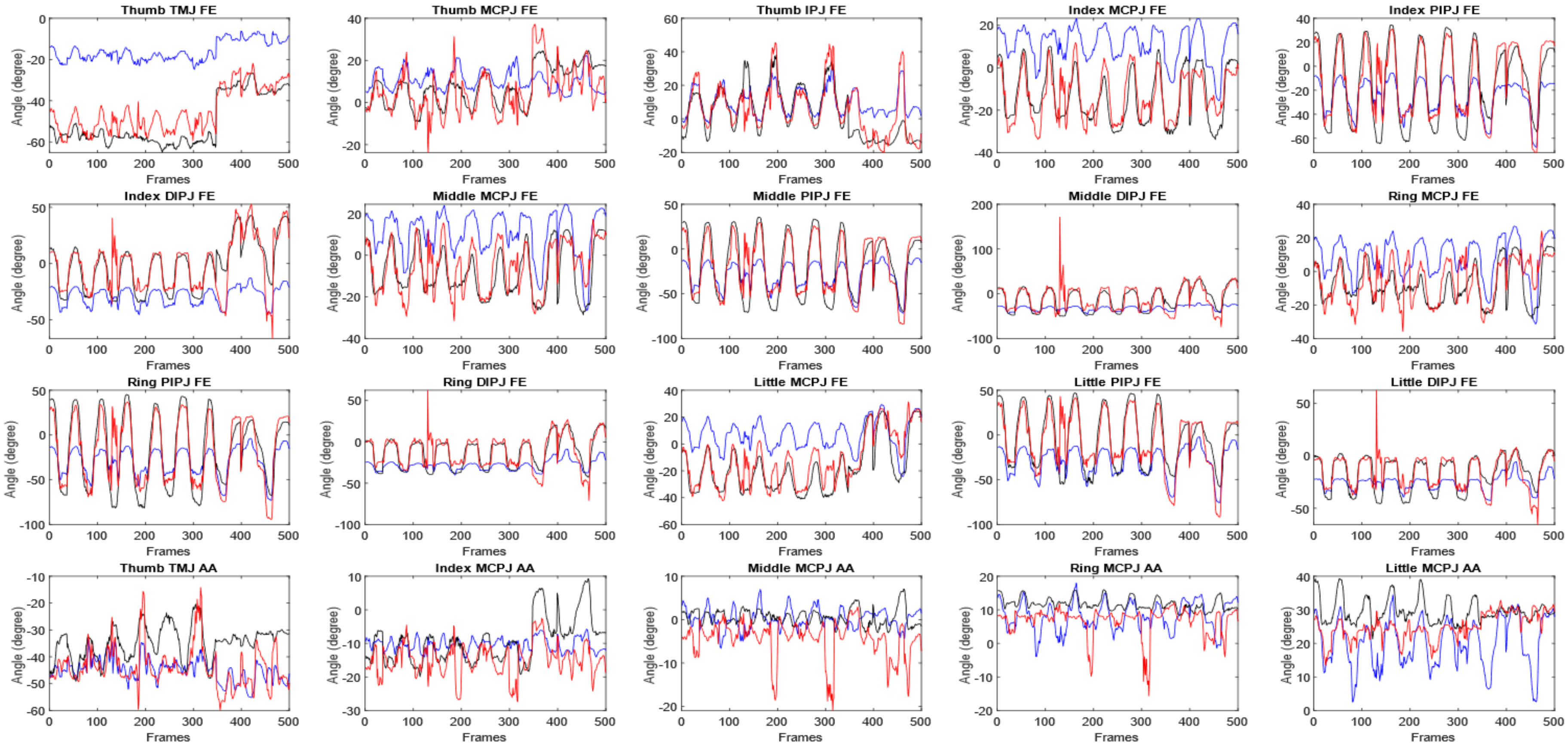
On the left, the RMSE between the input (LM) and target (Vicon) data is shown. On the right the RMSE between the NN output and Vicon data. The LM-Vicon correlation showed greater RMSE values (Mean: 18.74° ± 8.35°, Range: 3.62°- 42.12°) than the NN output -Vicon correlation (Mean: 12.79° ± 5.79°, Range: 3.87°- 37.77°). This suggests that the neural network successfully reduced the error of the LM. The RMSE was smallest for the abduction-adduction angles (row 16-20) in both correlation approaches, which is interesting considering that the correlations were weak and insignificant for these angles.

Percentage change RMSE



The percentage change in RMSE between the two methods (LM to Vicon and NN output to Vicon) was calculated. As the purpose of the NN method was to reduce the error of the LM, a negative value in the table indicates a reduced RMSE value. And positive value indicates an increased RMSE after for the NN output data relative to the LM raw data. On average the RMSE was reduced by 31%, which was found to be significant (p<0.001).

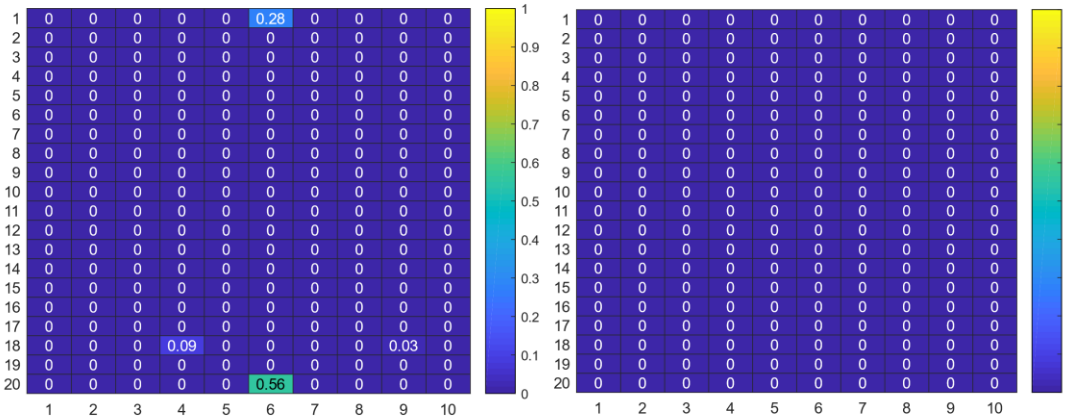
Angles



In the figure above a short example of angles from NN1 test phase (Frames 1:500) are shown. The difference of the magnitude of angles between the LM (blue) and Vicon (black) measurement options are evident explaining the large RMSE values. The NN prediction (red) is mostly closer to the target Vicon data, thus supporting the findings of reduced RMSE values after training. However, on several occasions, especially for the AA angles (bottom row), the NN curves show large errors in the estimation of angles. The reasons for this are unknown.

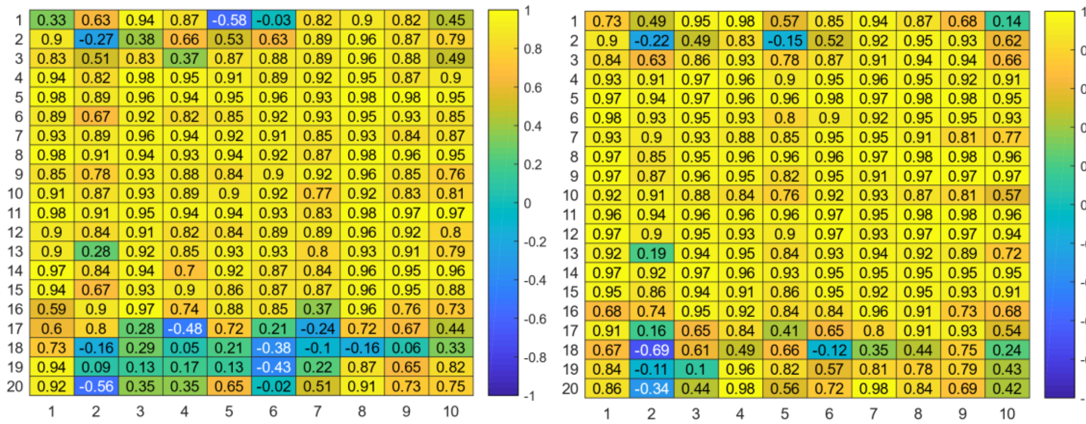
Right hand:

p-value:



On the left, the p-value for the input (LM) and target (Vicon) correlation is shown. On the right the p-value for the NN output-target correlation. Both LM and NN generated data is significantly correlated to the Vicon target data for most (LM to Vicon) or all (NN output to Vicon) angles (y-axis) and NNs (NN1 - NN10: x-axis). Contrary to the left hand, the NN output is significantly correlated for all joints in all NNs, suggesting differences in data sets or differences of the quality of input data. Similarly, to the left hand, the insignificant correlations for the LM to Vicon correlation data are mostly linked to abduction-adduction angles (row 16-20), which are only minorly moved in the flexion-extension movement the participants followed.

Correlation coefficient (R^2):



On the left, the correlation coefficient (R^2) for the input (LM) and target (Vicon) (mean R value: 0.73) correlation is shown and on the right R^2 for the NN output to Vicon correlation (mean R value: 0.81). In sum, both methods show similar strength of correlation for the flexion-extension angles (row 1-15).While FE angles show strong correlations in both approaches as indicated by the yellow shading, the abduction-adduction angles (row 16-20) show weak correlations for both the LM-Vicon comparison and NN output to Vicon, whereby the LM to Vicon correlations are weaker than the NN output to Vicon ones. This trend is supported by the finding on the left hand and is likely linked to the limited amount of movement in AA direction during the flexion-extension movement. Weak R^2 values further support the findings of the p-value table.

RMSE

	1	2	3	4	5	6	7	8	9	10
1	9.1	23.9	17.2	23.3	33.3	33.6	22.1	16.7	12.6	7.6
2	8.9	10	6.7	5.2	4.2	4.8	14.4	16.5	16.2	9.2
3	13.3	21.4	6.6	16.1	27.3	25.6	19.9	18.1	17.7	16.2
4	25.8	23.3	25	23.5	19.7	22.8	29.4	34	31	27.4
5	16.3	15.4	16.9	18.4	14.9	13.9	19.5	18.2	19	17.7
6	17.7	28.6	33.1	30.7	17.5	18.3	17.9	18.5	17.7	16.9
7	25.2	15.2	14.5	15.2	15	15.8	29.5	34.9	31.8	26.9
8	11.5	12.1	11.3	12.9	9.7	11.2	19.8	21.5	20.3	10.5
9	25	29.1	32.8	31	24.6	25.6	24.4	23.2	23.4	25.3
10	25.5	13.4	11.5	14.5	19.6	16.1	29.5	35.3	32.4	27.9
11	17	14.4	12.7	13.5	9.5	11.2	22.5	24.1	25.6	19.3
12	22.7	22	22.7	25.3	26.7	23.9	19.3	15.9	17.6	22.3
13	37.5	25.5	32.8	28.4	17.8	16.5	32.8	37.9	36.1	39
14	24.8	24.7	31.6	28.1	7.2	10.9	18.5	18.9	24.3	27.4
15	25.3	28.2	30.4	30.4	29.9	28.5	25.3	23.2	22.2	25.5
16	9.6	15.5	10.8	19.1	27.7	29.7	20.8	6.3	8.1	9.2
17	14.1	11.7	11.3	14.8	21.1	20	13.7	8.2	10.6	16.4
18	13	11.2	12.4	13.2	14.8	14.1	12	10.2	11	13.6
19	9.9	10.7	7.9	12.1	17.8	16.2	11.3	9.2	9.4	9.8
20	9.8	16.6	11.5	17	25.8	23.8	13.6	6.7	8.5	10.8

	1	2	3	4	5	6	7	8	9	10
1	5	17.6	7.1	4.5	7.1	4.1	7.1	6.4	7.9	7.9
2	5.8	13.6	4.5	3.9	7.2	8.1	8.2	6.9	6.9	5.3
3	4.4	16.3	5.3	4.4	9	7.3	5.6	6.5	6.6	7
4	6.9	12.1	6.3	8	7.7	4.3	5.6	4.7	6.2	4.3
5	5.1	7.2	4.9	5.8	7.3	7.2	6.6	5	5.2	6.7
6	3.5	8.6	6.9	7.8	8.7	6.7	6.5	4.4	5	6.8
7	6.1	16.7	10.2	10.8	9.1	6.5	7.2	6.6	10	7.6
8	6.4	12.5	6.4	6.7	7.2	9.6	7	6.6	6.5	6.1
9	4.9	11.8	6.1	5.9	7.6	6.5	8	4.3	5.1	7.8
10	5.7	16.5	12.1	11.8	9.6	9.7	10.9	7.4	9.9	9.8
11	7	8.7	7.7	7.8	7	9.6	10.8	7.1	7	8.4
12	4.9	9.2	6.8	7.3	11.4	9.9	8.5	4.4	4.8	10.1
13	4.1	28.4	8.7	10.3	14.3	13.2	10.4	7.2	8.1	6.9
14	4.9	14.2	5.8	7.4	7.2	10.8	8.8	6.9	7.9	6.8
15	5.7	9.7	5.7	6	10.6	8.4	11	6.4	7.9	12.5
16	10.9	24.1	13.3	12.9	12.4	16	10.9	9.6	11.8	11.4
17	13	11.6	11	11.4	11.3	10.1	11.7	11.3	12	10.7
18	11.9	10.6	9.7	9.8	9.5	8.6	10.5	10.5	11.1	11.3
19	11.9	12.8	10.1	10.4	11.2	9.2	10.8	11.9	12.6	11.5
20	12.8	18.6	14.1	13.8	12.8	10.7	10.3	11.5	14.3	13.3

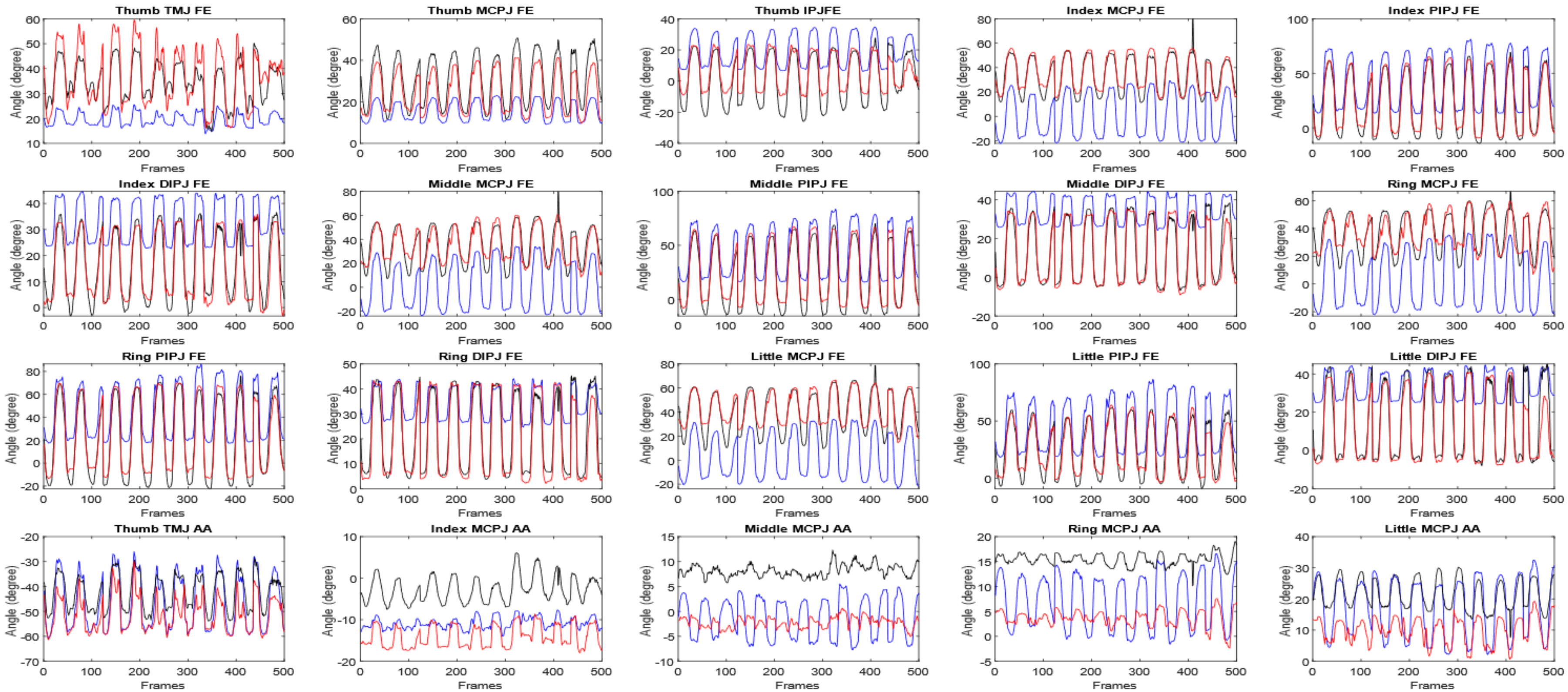
On the left, the RMSE between the input (LM) and target (Vicon) data is shown and on the right the RMSE between the NN output Vicon data. The LM-Vicon comparison showed greater RMSE values (Mean: 19.21° ± 7.91°, Range: 4.19°- 38.99°) than the NN output to Vicon comparison (Mean: 8.89° ± 3.49°, Range: 3.46°- 28.41°). This suggests that the neural network successfully reduced the error of the LM. The RMSE was smallest for the abduction-adduction angles (row 16-20) for the LM to Vicon comparison, and the NN approach showed conflicting effects on the RMSE magnitude for these joints, decreasing some RMSE values while increasing others.

Percentage change RMSE

	1	2	3	4	5	6	7	8	9	10
1	-44.8	-26.4	-58.9	-80.5	-78.6	-87.8	-67.8	-61.8	-37.1	3.8
2	-34.5	36.6	-33.3	-26.1	71.7	67.6	-43.3	-58	-57.5	-42.2
3	-67.1	-24	-19.1	-72.4	-67	-71.6	-71.9	-64.1	-62.8	-56.9
4	-73.3	-47.9	-74.6	-66	-60.9	-81.1	-81	-86.1	-80.1	-84.3
5	-68.7	-53.6	-71.2	-68.4	-50.7	-47.9	-66	-72.5	-72.8	-62.1
6	-80.5	-70	-79.1	-74.5	-50.6	-63.4	-63.6	-76.4	-72	-59.8
7	-75.8	9.5	-29.3	-29.1	-39.6	-58.9	-75.5	-81	-68.4	-71.7
8	-44.4	3.2	-42.8	-48.3	-26.4	-14.8	-64.6	-69.2	-68	-42
9	-80.6	-59.2	-81.5	-80.9	-69.1	-74.6	-67.3	-81.6	-78.4	-69.4
10	-77.8	23.5	5.4	-18.7	-51	-39.5	-62.9	-79	-69.4	-64.7
11	-58.5	-39.2	-39.9	-41.9	-26	-14	-52.2	-70.4	-72.8	-56.5
12	-78.4	-58.2	-70.2	-71.2	-57.3	-58.4	-55.6	-72.4	-72.5	-54.6
13	-89.2	11.5	-73.4	-63.8	-19.6	-20	-68.3	-80.9	-77.5	-82.3
14	-80.2	-42.6	-81.6	-73.6	0.7	-0.7	-52.3	-63.3	-67.4	-75.1
15	-77.5	-65.6	-81.3	-80.4	-64.3	-70.6	-56.5	-72.2	-64.3	-51.1
16	13.7	55.6	23	-32.3	-55.3	-46	-47.6	51.5	46.5	24.6
17	-8.3	-0.9	-2.2	-22.9	-46.7	-49.7	-14.4	38.5	13.1	-34.9
18	-8.4	-5.4	-21.6	-25.5	-35.8	-38.8	-12.2	2.8	0.9	-16.8
19	20.7	19.9	27.1	-13.8	-37	-43.3	-4.4	29.2	34.4	17.6
20	30.5	12.1	22.2	-18.8	-50.6	-55.1	-23.8	70.4	69	23.9

The percentage change in RMSE between the two methods (LM to Vicon and NN output to Vicon) was calculated. As the purpose of the NN method was to reduce the error of the LM, a negative value in the table indicates a reduced RMSE value. And positive value indicates an increased RMSE for the NN output data relative to the LM raw data. On average the RMSE was reduced by 54%, which was found to be significant ($p<0.001$). However, the abduction-adduction angles (row 16-20 show very conflicting evidence, which might be linked to the limited amount of movement in these joints.

Angles



In the figure above a short example of angles from NN1 test phase (Frames 1:500) for the right-hand flexion-extension movement are shown. The difference of the magnitude of angles between the LM (blue) and Vicon (black) measurement options are evident explaining the large RMSE values. Important to note is that despite the large difference in magnitude, the LM and Vicon measurements follow the same pattern, but at an offset. Therefore the correlations are strong for the flexion-extension angles, but not the AA angles. The NN prediction (red) is mostly closer to the target Vicon data, thus supporting the findings of reduced RMSE values after training. Especially for the AA angles (bottom row), the NN curves show poor agreement to the Vicon data.

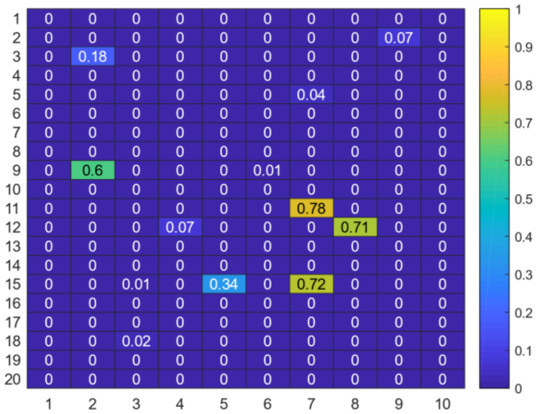
Appendix 4:

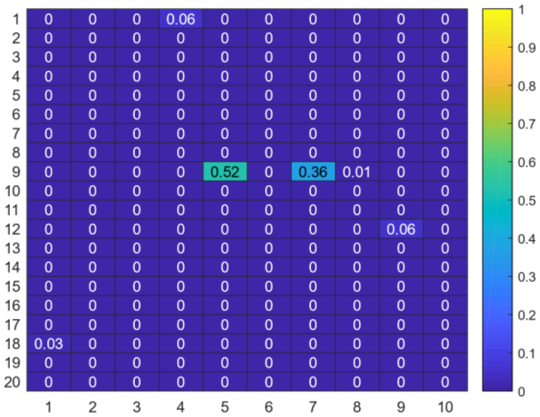
Application of an artificial neural network to predict joint centres and subsequently angles of finger joints during abduction-adduction movement

Following the same protocol as outlined in chapter 6, a task specific neural network for the left and right hand was generated, trained and tested. The results were assessed using the same methods as outlined in Chapter 6, but the hands were trained and evaluated separately. In this appendix the ability to measure and predict abduction-adduction movements is evaluated.

Left hand:

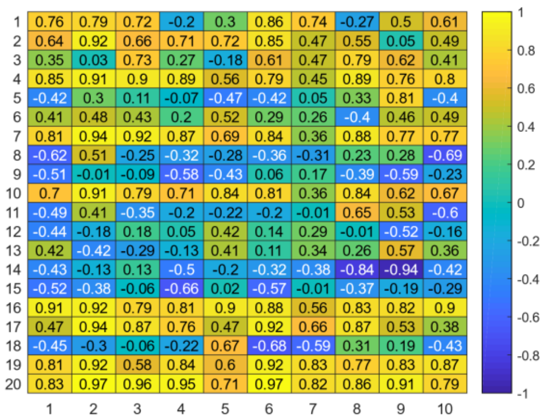
p-value:

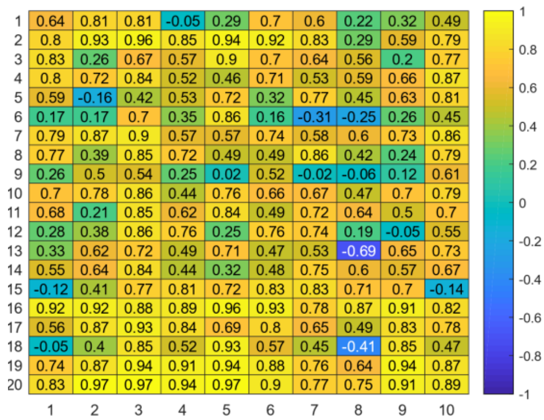




On the left, the p-value for the input (LM) to target (Vicon) correlation is shown and on the right the p-value for the NN output to Vicon correlation. Both methods show mostly significant correlations. All insignificant correlations for both methods are for flexion-extension angles (rows 1-15), while all abduction-adduction angles (16-20) are significantly correlated. This might be linked to abduction-adduction being the primary movement in the analysed task.

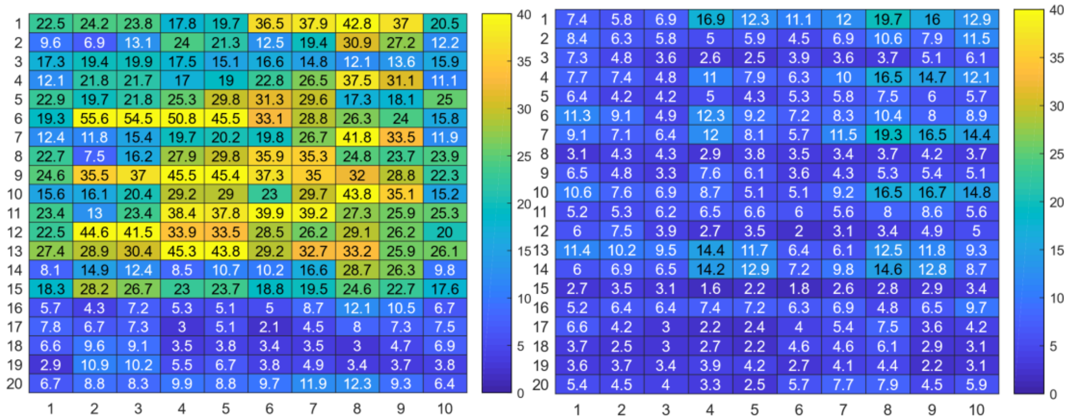
Correlation coefficient (R^2):





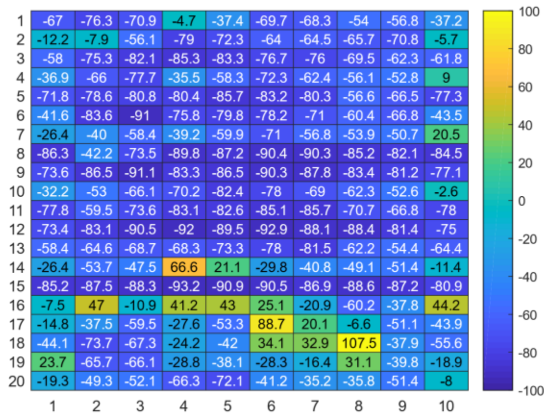
On the left, the correlation coefficient (R^2) for the input (LM) and target (Vicon) correlation (mean R value: 0.30) is shown and on the right R^2 for the NN output to Vicon correlation (mean R value: 0.61). In particular for the FE angles (rows 1-15) the LM to Vicon data shows weaker correlations than the NN output and Vicon data as indicted by the change in shading of the cells. Important to notice are also some negative correlations for the Middle MCP joint abduction adduction angle (row 18) in both methods. The reason for this is unclear.

RMSE



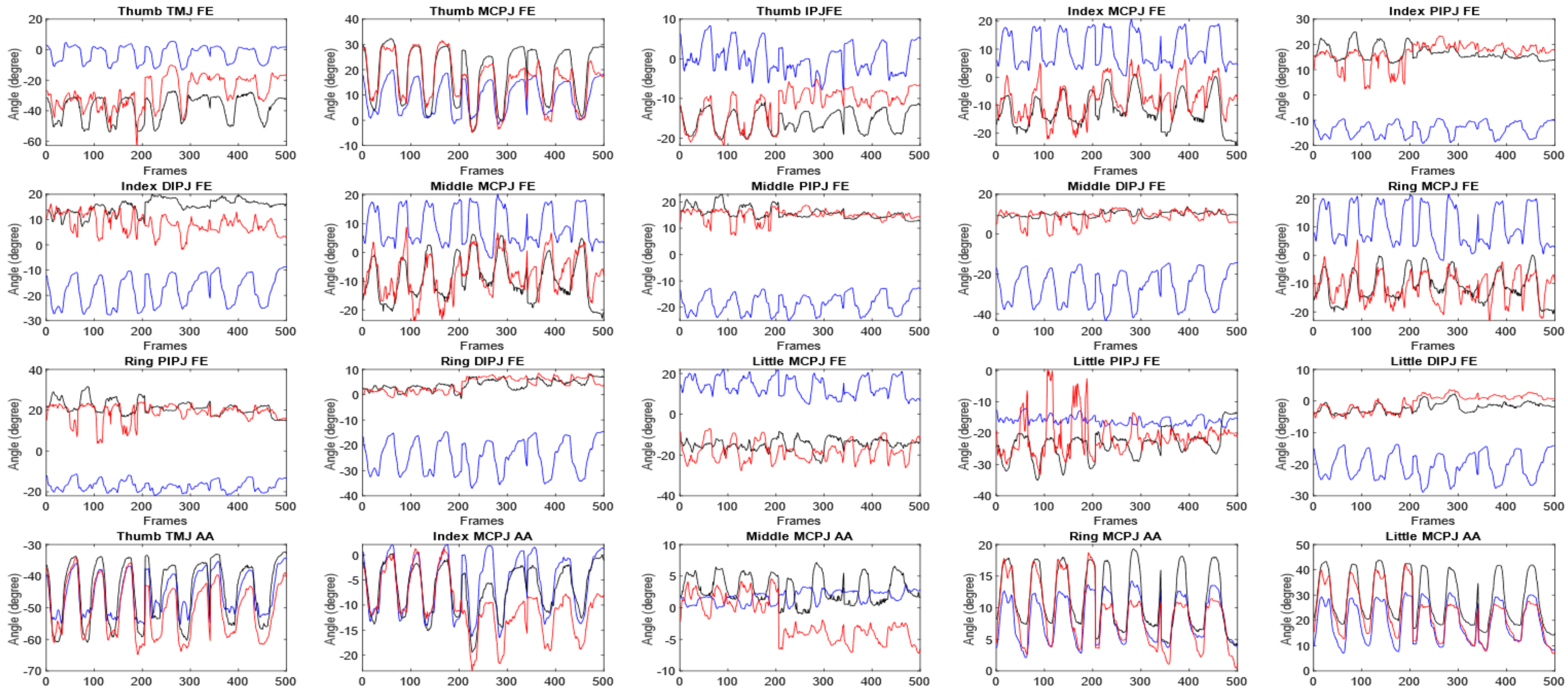
On the left, the RMSE between the input (LM) and target (Vicon) data is shown and, on the right, the RMSE between the NN output Vicon data. The LM-Vicon comparison showed greater RMSE values (Mean: 20.61° ± 11.98°, Range: 2.13°- 55.59°) than the NN output -Vicon comparison (Mean: 6.73° ± 3.74°, Range: 1.57°- 19.68°). This suggests that the neural network successfully reduced the error of the LM on average. The RMSE values for the flexion-extension angles (row 1-15) of the LM to Vicon comparison were greater than the abduction-adduction related angles (row 16-20), which supports the findings from the flexion-extension approaches. The NN approach could successfully reduce the large RMSE values of the flexion-extension angles as indicated by the change of colour in the table.

Percentage change RMSE



The percentage change in RMSE between the two methods (LM to Vicon and NN output to Vicon) was calculated. As the purpose of the NN method was to reduce the error of the LM, a negative value in the table indicates a reduced RMSE value. And positive value indicates an increased RMSE after for the NN output data relative to the LM raw data. On average the RMSE was reduced by 67%, which was found to be significant ($p<0.001$). While the RMSE was reduced for the flexion-extension angles (row 1-15), changes for the abduction-adduction angles are conflicting. Most AA-angles show a reduced RMSE in the NN to Vicon data set, yet for some the error increased. This might be linked to the already small RMSE of the LM to Vicon data and the large discrepancies for the flexion-extension angles, leading to an overestimation of abduction-adduction movements.

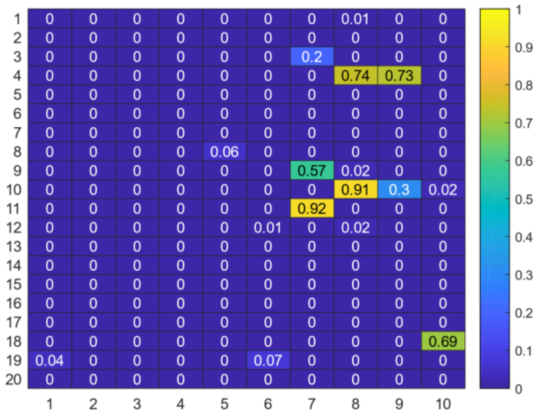
Angles

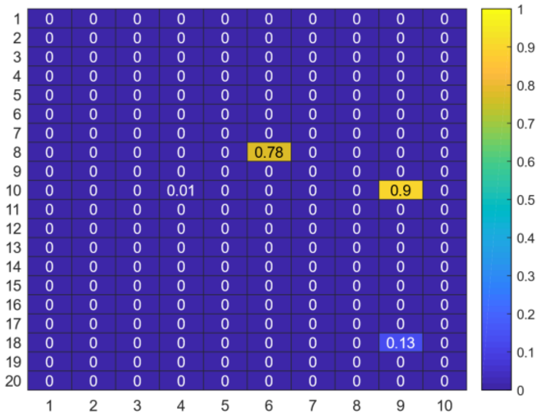


In the figure above a short example of angles from NN1 test phase (Frames 1:500) are shown. The difference of the magnitude of angles between the LM (blue) and Vicon (black) measurement options are evident explaining the large RMSE values. Yet the curves follow similar pattern at an offset, which explains the moderate to strong correlations between LM and Vicon data. The NN prediction (red) is mostly closer to the target Vicon data, thus supporting the findings of reduced RMSE values after training. But the red curve frequently over or underestimates the magnitude of angles as measured with the Vicon system. The Middle MCP joint abduction adduction angle showed negative correlation, and in this angle finger large discrepancies between the red curve relative to both the LM (blue) and Vicon (black) curve are visible, despite neither the LM nor the Vicon curve changing pattern. The reason for these errors remains unclear.

Right hand:

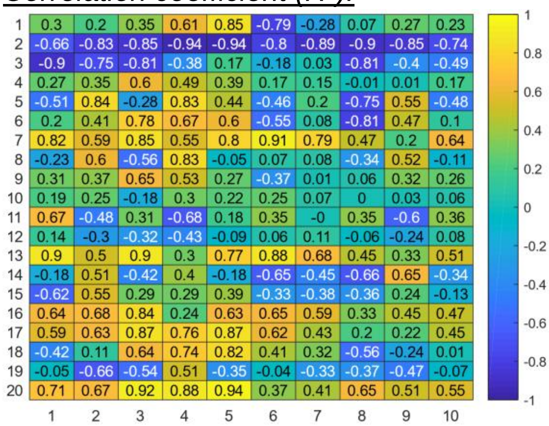
p-value:

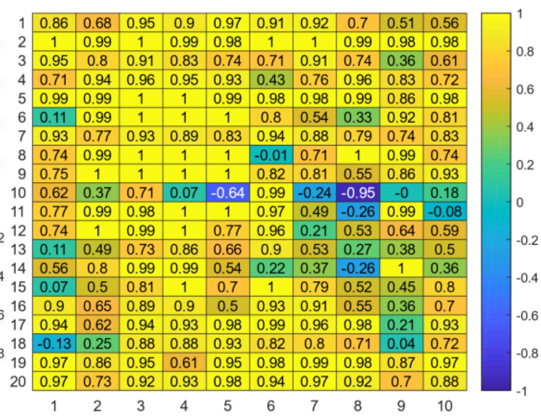




On the left, the p-value for the input (LM) to target (Vicon) correlation is shown and on the right the p-value for the NN output to Vicon correlation. Both methods show mostly significant correlations, whereby the NN output to Vicon data shows more significant correlations. Most insignificant correlations for both methods are for flexion-extension angles (rows 1-15), while abduction-adduction angles (16-20) are significantly correlated, with the exception of the Middle MCP joint for the 10th data split (x-axis) of the LM to Vicon data set and the 9th data split for the NN output to Vicon data. The weak correlations support findings from the left hand and again, may be linked to abduction-adduction being the primary movement.

Correlation coefficient (R^2):





On the left, the correlation coefficient (R^2) for the input (LM) and target (Vicon) correlation (mean R value: 0.13) is shown and on the right R^2 for the NN output to Vicon correlation (mean R value: 0.74). The LM to Vicon data shows mostly very weak to moderate correlations, and some strongly negative (mostly row 2: Thumb MCP joint flexion extension). The reason for this is unknown, however it appear that the NN can rectify this poor correlation. The NN output indicates some perfect correlation (R^2 = 1) and shows generally greater strength of correlation as indicated by the shading of the cells.

__RMSE__

	1	2	3	4	5	6	7	8	9	10
1	70.7	80.4	77.3	77.8	73.4	96.1	90.1	82.7	82.5	78.9
2	67.7	84.6	87.1	104.8	92.6	75.3	79.6	71.5	77.8	68.7
3	19.9	20.9	34	33.4	32.8	17.7	16.9	18.7	19.6	19.2
4	70.9	53.2	54.8	47.9	43.3	59.4	58.4	62.4	71.7	75.1
5	35.6	32.8	75.1	31.3	49.5	23.8	31.4	35.2	29.9	30.7
6	57.5	61.7	61	56.4	56.3	59.3	61.2	59.7	61.6	60
7	53.1	43.6	46	44	37.6	30	36	38.6	63	55.8
8	55	41.4	74.5	26.1	55.8	52.1	50.8	54.6	40.7	55.2
9	61.6	65.7	63.1	60.4	66	60.7	63.4	62.6	67.1	61.8
10	68.6	60.8	64.7	64.6	64	45.2	52.4	54.8	77.3	71
11	53.3	64	53.3	82	58.5	24.5	47.5	46.5	65	51.7
12	49.4	54.2	49.8	55.6	60.4	35.3	51.7	55.7	52.5	52.1
13	58.9	34.3	47.2	42.9	27.3	36.8	34.6	26.8	67.2	61.3
14	70.2	53.1	77.5	40.8	56.9	84.2	77.1	73.6	52.1	70.8
15	73.7	56.6	66.6	64.6	71.4	56.6	60.8	56.8	67.4	60.5
16	18.2	11	7	14.9	6.3	16.4	13.3	11.8	16.7	19.3
17	19.3	22.3	16.5	14.9	13.8	27.8	24.3	26.4	17.1	19.7
18	15.9	26.7	19.9	18.7	18.8	33.1	28.5	22.9	13	15
19	19.8	28.6	24.2	19.6	20.6	36.4	32.6	30.2	15.7	19.6
20	19.1	26	25.9	20.4	19.2	38.6	31.8	26.3	18.7	21.5

	1	2	3	4	5	6	7	8	9	10
1	22.2	13.6	16.5	11.5	5.1	23.1	15	10.8	16.7	15.9
2	5.5	7.4	5.5	9.2	13.1	4.1	3.8	9.5	11.7	10.7
3	2.8	5.5	8	4.6	6	5.5	2.6	4.3	10	6.7
4	30.7	7.7	6.6	6.8	10.6	60.3	31.7	10.5	16.6	28
5	4.7	5.4	2.9	2.5	4.2	3	5	3.9	16.5	4.3
6	76	7.2	8.3	3.9	4.1	35	54.9	65.8	20.5	35.4
7	19	11.3	6.4	9	10.7	8.3	11	8.2	16.6	12.9
8	39	8.3	3.3	3.4	4.2	67.8	36.8	3.8	8.1	38
9	41.2	4.8	5.3	2.3	1.6	34.2	35.3	56.1	27.6	21.9
10	54.6	70.6	49.3	80.3	104.3	9.5	82.6	107.9	89	77.2
11	31.8	10.9	8.5	3.5	3.4	9.6	43.6	78.8	8.7	68.6
12	29.2	5.3	5.5	2.1	38.3	8.2	57.3	48.5	46.2	39.2
13	25.5	21.2	9	11.4	10.3	7.6	11.9	14.9	18.3	16.3
14	55.7	36.1	9.8	6.7	50.8	65.1	64.2	93.9	7.1	68.5
15	80.1	56.4	31.8	2.4	40.1	2.7	37.2	56.4	58.2	36.5
16	12.1	16.2	13.1	11.2	11.7	11	9.6	15.5	11.9	10.6
17	17.7	10.2	11.1	11.1	10.6	8.1	10.2	10.9	18.4	13.7
18	19.6	9.1	7.8	10.6	10	7.1	8.2	9.6	17.8	13.9
19	16.4	8.5	5.7	11.1	10.2	7.8	9.2	6	18.8	14.3
20	14.6	7.6	7.2	12.4	9.5	8.9	10.3	8.2	18.5	15.1

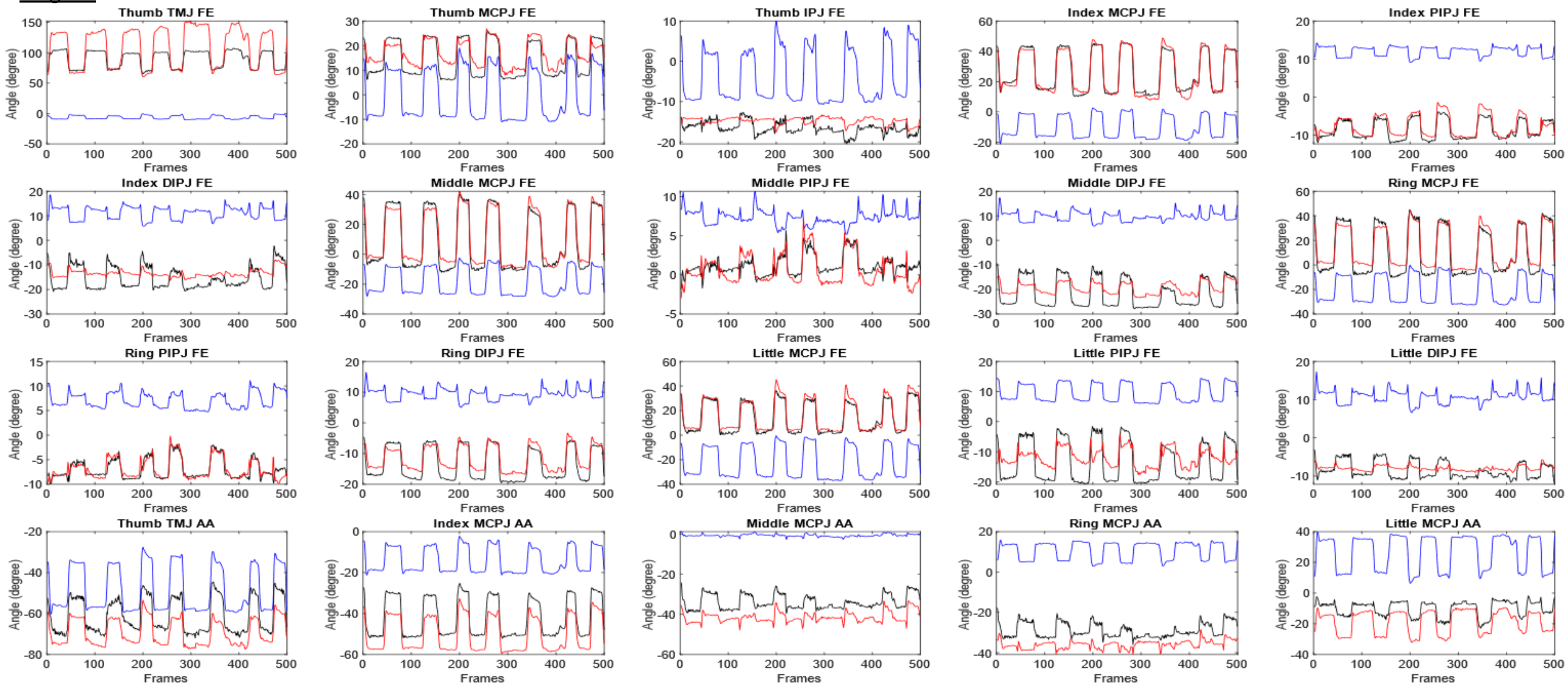
On the left, the RMSE between the input (LM) and target (Vicon) data is shown and, on the right, the RMSE between the NN output Vicon data. The LM-Vicon comparison showed greater RMSE values (Mean: 47.33° ± 21.99°, Range: 6.31°- 104.80°) than the NN output -Vicon comparison (Mean: 21.37° ± 22.58°, Range: 1.56°- 107.86°). This suggests that the neural network successfully reduced the error of the LM on average. The RMSE values for the flexion-extension angles (row 1-15) of the LM to Vicon comparison were much greater than the abduction-adduction related angles (row 16-20), similar to the pattern identified at the left hand. The NN approach could successfully reduce the large RMSE values for many flexion-extension angles as indicated by the change of colour in the table, yet some sizeable RMSE values remain. The AA angles showed smaller RMSE values between the LM and Vicon data, and these could mostly be further reduced by the NN approach.

__Percentage change RMSE__

	1	2	3	4	5	6	7	8	9	10
1	-68.6	-83.1	-78.6	-85.2	-93	-76	-83.3	-86.9	-79.8	-79.9
2	-91.9	-91.2	-93.7	-91.2	-85.8	-94.5	-95.2	-86.7	-85	-84.5
3	-86.1	-73.6	-76.6	-86.2	-81.7	-68.8	-84.6	-76.9	-49.1	-65.3
4	-56.8	-85.4	-88	-85.7	-75.6	1.4	-45.7	-83.2	-76.8	-62.7
5	-86.9	-83.6	-96.1	-92.1	-91.5	-87.4	-84.2	-88.9	-44.7	-85.8
6	32.1	-88.4	-86.4	-93.1	-92.7	-41	-10.3	10.1	-66.7	-41
7	-64.3	-74.1	-86.2	-79.5	-71.5	-72.3	-69.5	-78.6	-73.6	-76.8
8	-29	-79.9	-95.5	-86.8	-92.5	30.3	-27.4	-93.1	-80	-31.2
9	-33.2	-92.6	-91.5	-96.2	-97.6	-43.8	-44.3	-10.4	-58.9	-64.6
10	-20.4	16.3	-23.8	24.3	62.9	-78.9	57.7	96.9	15.1	8.7
11	-40.4	-82.9	-84	-95.7	-94.2	-60.8	-8.3	69.5	-86.5	32.6
12	-40.9	-90.2	-89	-96.3	-36.7	-76.9	10.9	-12.9	-12.1	-24.8
13	-56.7	-38.1	-81	-73.4	-62.4	-79.4	-65.5	-44.5	-72.7	-73.4
14	-20.6	-32.1	-87.3	-83.6	-10.8	-22.6	-16.7	27.5	-86.3	-3.2
15	8.8	-0.3	-52.2	-96.2	-43.8	-95.2	-38.7	-0.6	-13.6	-39.7
16	-33.7	46.7	87.2	-24.8	85.1	-32.7	-27.9	31.1	-29	-45.2
17	-8.1	-54.1	-33.1	-25.4	-23.1	-70.8	-58	-58.7	7.1	-30.6
18	23.7	-66	-60.5	-43.5	-46.7	-78.5	-71.1	-58.2	36.5	-7
19	-17.3	-70.4	-76.3	-43.5	-50.4	-78.6	-71.7	-80.1	19.9	-26.9
20	-23.7	-70.8	-72.3	-39	-50.4	-76.9	-67.5	-68.8	-1.4	-29.5

The percentage change in RMSE between the two methods (LM to Vicon and NN output to Vicon) was calculated. As the purpose of the NN method was to reduce the error of the LM, a negative value in the table indicates a reduced RMSE value. And positive value indicates an increased RMSE after for the NN output data relative to the LM raw data. On average the RMSE was reduced by 55%, which was found to be significant ($p<0.001$). While the RMSE was reduced for most angles the magnitude of chance varied greatly. The reasons for the inconsistent changes in RMSE by the neural network approach cannot be explained at this stage.

Angles



In the figure above a short example of angles from NN1 test phase (Frames 1:500) are shown. The difference of the magnitude of angles between the LM (blue) and Vicon (black) measurement options are evident explaining the large RMSE values. Yet, just as seen before on the left hand and for flexion-extension angles, the curves follow similar pattern at an offset. The NN prediction (red) is mostly closer aligned to the target Vicon data, thus supporting the findings of reduced RMSE values after training, but the red curve is for three of the abduction-adduction angles (bottom row) overestimating the angle magnitude, as the red line is on the opposite site of the black curve relative to the blue line (LM, input data). Flexion-extension curves from the Vicon data are irregular, which the LM data does not support. This might be due to modelling, and could explain the RMSE and R^2 values of this data set.

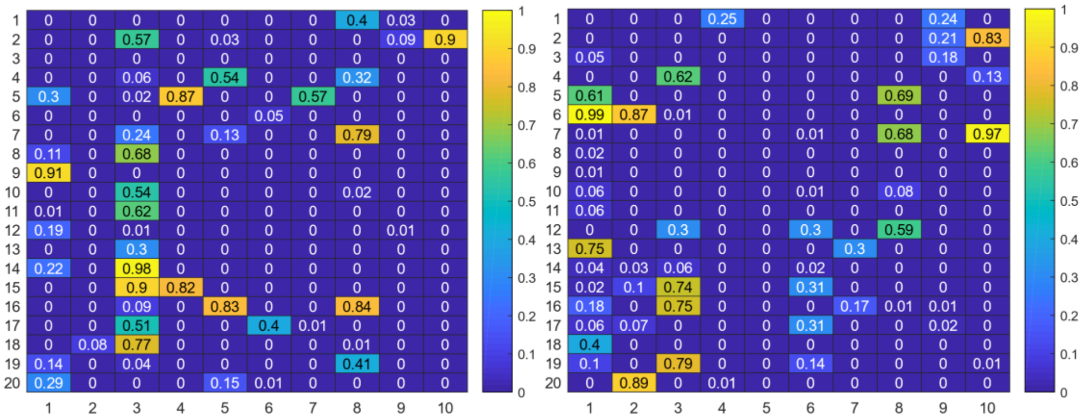
Appendix 5:

Application of an artificial neural network to predict joint centres and subsequently angles of finger joints during thumb circumduction movement

Following the same protocol as outlined in chapter 6, a task specific neural network for the left and right hand was generated, trained and tested. The results were assessed using the same methods as outlined in Chapter 6, but the hands were trained and evaluated separately. In this appendix the ability to measure and predict thumb-circumduction movements is evaluated.

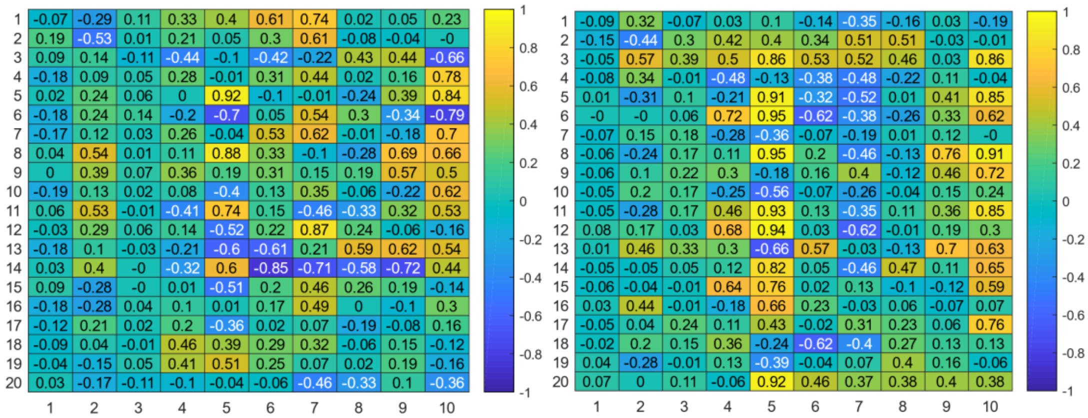
Left hand:

p-value:



On the left, the p-value for the input (LM) to target (Vicon) correlation is shown and on the right the p-value for the NN output to Vicon correlation. There are 34 insignificant correlations for both approaches, but not for the same angles (y-axis) or 10% data splits (x-axis). In comparison to abduction-adduction and flexion-extension movements there are many more insignificant correlations. As only the thumb is moving in this circumduction trial, most attention should be given to the angles of the thumb (Flexion-Extension angles of the TM (row 1), MCP (row 2) and IP (row 3) joints and Abduction adduction of the TM joints (row 16). Yet even for the thumb joint angles there are insignificant correlations.

Correlation coefficient (R^2):



On the left, the correlation coefficient (R^2) for the input (LM) and target (Vicon) correlation (mean R value: 0.08) is shown and on the right R^2 for the NN output to Vicon correlation (mean R value: 0.13). For both approaches' correlations are mostly very weak to moderate, which is in conjunction with the findings in the p-value table.

RMSE

	1	2	3	4	5	6	7	8	9	10
1	20.1	64	18.7	14.4	12.6	15.2	9.6	33.7	28.4	23.7
2	12.5	45	9.6	9.8	11.9	14.7	14.2	12.4	11.8	11.5
3	8.1	14.6	28.8	22.8	19.8	16	18.7	19	29.7	30.4
4	14	36.2	35.2	21.8	13.3	12.3	17	49.7	48.2	29.7
5	37.1	41.2	20.8	18.2	19.5	21.4	20.8	45.1	54	48.5
6	11.8	28.5	26.9	60.9	42	18	22.9	48.4	51.6	38.1
7	9.6	39.9	42.3	18.3	14.3	15.3	19.1	57.3	57.6	36.8
8	31.7	35.8	23.3	14	20.1	24.3	21.5	45.5	53.2	45.4
9	21.7	25.4	28.4	40.9	31.8	26.3	31.7	46.9	47.9	34.1
10	10	43.3	45.5	17.5	10.4	10.5	14.5	57.1	59.3	38.5
11	30.8	43.8	28.9	21.2	22.1	26.9	27.2	50.2	58.2	47.8
12	20.1	24.6	27.3	43.1	32.2	20.1	25.6	46.3	45.5	34.3
13	12.5	49.2	51.4	21.3	7.2	7.1	15.7	32.1	44.1	37.2
14	31.8	50.7	29	36.4	20.9	22.4	32.3	54.3	64.1	51.5
15	14.7	34.9	24.8	30	24.4	16.6	21.4	35.8	37.2	28.4
16	32	47.5	25.9	16.9	15.2	13.2	10	32.1	39.8	38.6
17	26.2	26.1	15.8	15.7	24.4	27.2	23.2	20.5	18.8	21.9
18	17.2	22.1	24.3	16.4	22.8	24.1	20.2	23	19.9	19
19	15.1	41.5	23	22.1	23.9	22.5	19.9	21.5	19.5	14.9
20	19.4	55.3	19.4	11.6	12.2	14.3	15.1	31.7	39.4	32.5

	1	2	3	4	5	6	7	8	9	10
1	33.8	53.8	10.7	13.9	17.7	19.6	21.5	21.9	16.6	29.3
2	20.9	44.9	10.4	9.3	9.9	13.3	13.3	8.1	11.8	17.5
3	6.4	12.9	9	3.9	3.2	2.6	4.1	6.5	5.7	5.5
4	35.3	19.4	15.9	20.6	11.3	10.8	12.2	12.9	10.4	23
5	13.2	43.1	19.9	7.3	4.8	4.8	10.8	15.7	8	10.3
6	8.1	20.5	6.2	18	11.5	6	4	5	5.3	8.4
7	20.6	22	19.2	28.4	15.7	8.4	10.3	12.2	9.4	15.5
8	10.9	26.8	14.7	11.5	4.4	5.7	10	9.4	5.7	8.1
9	2.4	13.7	3.1	4.1	4.5	1.9	1.9	4.6	3.4	4.3
10	19.2	29	20.2	23.5	13.1	8.3	10.8	13.1	9.6	14.3
11	15.4	39.8	18.7	6.9	5	7.7	14.9	12.2	8.8	10.8
12	3.1	10.8	2.5	10.2	6.6	3.3	5.2	2.8	2.7	5.5
13	19.2	40.6	22.1	19	17.2	8.5	12.4	10.4	10.3	13.2
14	20	51	18.8	9.4	7.7	5.8	12.3	15.4	13.1	13.3
15	5.8	6.8	3.4	2	3.8	2.5	3.3	3.3	3.7	3.5
16	16.6	54.6	18.4	19.2	13	8.9	12.7	10.4	15.4	15.6
17	7.6	34.4	5.7	7.8	9.2	6.3	5.8	7	5.5	5.4
18	4.6	14.1	12.2	7.5	9.3	9.3	3.5	7.1	4.6	4.7
19	9.5	34	15.5	12.9	10.6	10.3	4.3	6.6	5.4	8.4
20	18.2	60.4	10.1	12.7	9.2	12	9.3	8.7	10.6	14.6

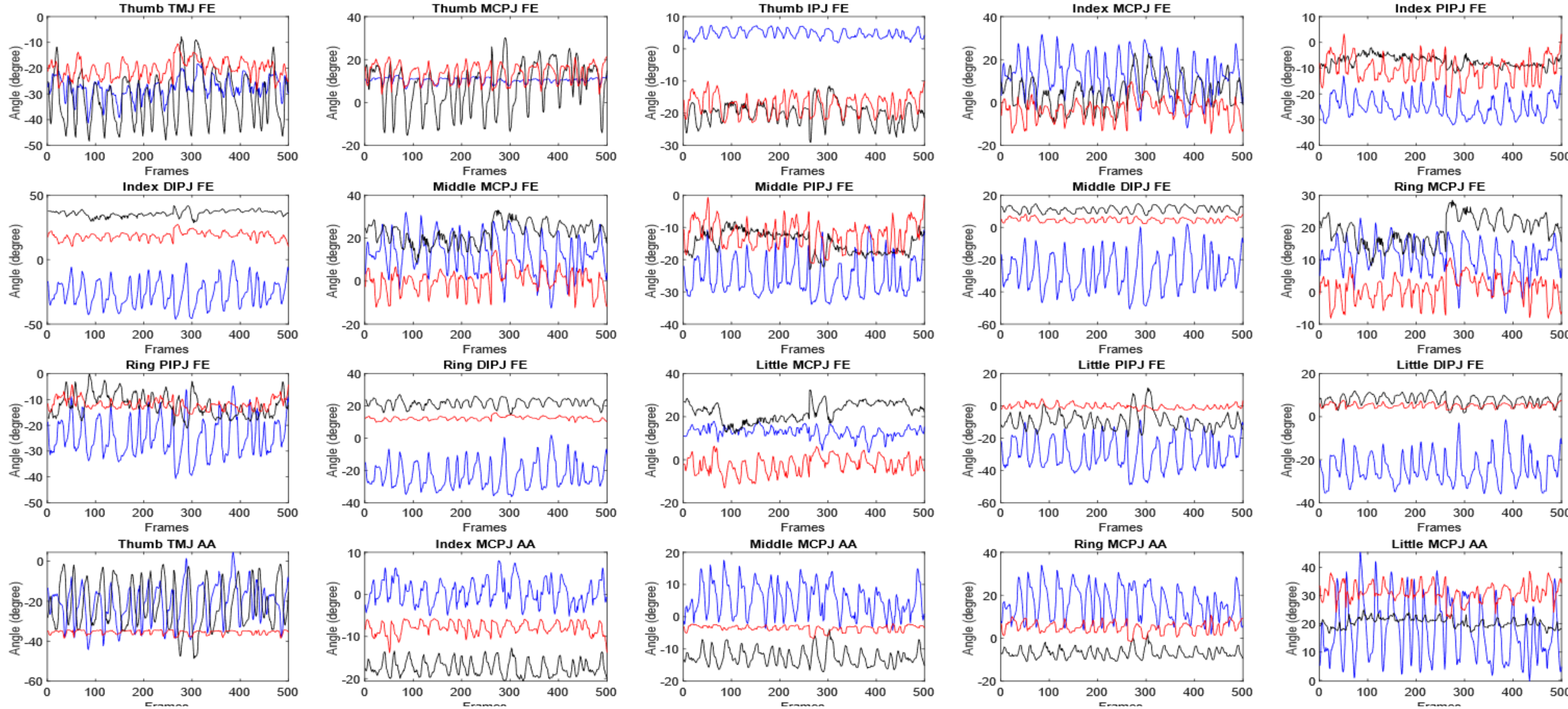
On the left, the RMSE between the input (LM) and target (Vicon) data is shown and, on the right, the RMSE between the NN output Vicon data. The LM-Vicon comparison showed greater RMSE values (Mean: 28.06° ± 13.63°, Range: 7.08°- 64.1°) than the NN output -Vicon comparison (Mean: 12.73° ± 10.03°, Range: 1.90°- 60.45°). This suggests that the neural network successfully reduced the error of the LM on average, but the pattern from the flexion-extension and abduction adduction movements, indicating that the predominantly moving joints are better predicted, is not supported by the RMSE for thumb circumduction.

Percentage change RMSE

	1	2	3	4	5	6	7	8	9	10
1	68	-16	-42.8	-4.1	40.6	28.5	123.7	-35	-41.6	23.5
2	67.6	-0.4	7.4	-4.3	-16.1	-9.7	-6	-34.2	0.1	52
3	-20.9	-11.8	-68.7	-83	-84	-83.7	-78.1	-65.7	-80.7	-82
4	151.8	-46.4	-54.8	-5.6	-15.1	-12.5	-27.9	-74	-78.4	-22.5
5	-64.3	4.7	-4.4	-59.9	-75.5	-77.5	-47.9	-65.2	-85.1	-78.7
6	-31.1	-28.3	-77	-70.4	-72.6	-66.6	-82.4	-89.7	-89.8	-77.9
7	114	-44.9	-54.7	55.5	9.8	-45	-46.3	-78.8	-83.7	-57.8
8	-65.7	-25.2	-37	-17.5	-78.1	-76.5	-53.6	-79.3	-89.2	-82.3
9	-89.2	-46	-89	-90	-85.7	-92.6	-94	-90.1	-92.9	-87.4
10	92.1	-33	-55.6	34.4	26.2	-21.5	-25.4	-77	-83.7	-62.7
11	-49.9	-9	-35.4	-67.2	-77.2	-71.4	-45.2	-75.7	-84.9	-77.4
12	-84.4	-56.3	-90.7	-76.3	-79.6	-83.8	-79.6	-93.9	-94	-84.1
13	53.7	-17.4	-57	-10.6	137.8	20.7	-21	-67.7	-76.6	-64.5
14	-37	0.7	-35.2	-74.3	-63.3	-74.3	-61.8	-71.5	-79.5	-74.2
15	-60.3	-80.4	-86.4	-93.4	-84.5	-84.7	-84.4	-90.8	-90.2	-87.7
16	-48.3	14.9	-28.9	13.4	-14.7	-32.6	28	-67.5	-61.3	-59.6
17	-71	32.1	-63.6	-50.2	-62.3	-76.8	-75.2	-65.8	-71	-75.3
18	-73.3	-36.2	-49.9	-54.3	-59	-61.5	-82.8	-69	-76.8	-75.4
19	-37.2	-18.2	-32.8	-41.4	-55.7	-54.3	-78.5	-69.2	-72.4	-43.2
20	-6.5	9.3	-47.9	9.2	-24.8	-15.7	-38.5	-72.6	-73	-55.1

The percentage change in RMSE between the two methods (LM to Vicon and NN output to Vicon) was calculated. As the purpose of the NN method was to reduce the error of the LM, a negative value in the table indicates a reduced RMSE value. And positive value indicates an increased RMSE after for the NN output data relative to the LM raw data. On average the RMSE was reduced by 55%, which was found to be significant ($p<0.001$). In the flexion-extension and abduction-adduction movements, the RMSE of the predominantly moving joints was typically reduced by the NN application. Here, for thumb circumduction, the RMSE frequently increases for the primarily moving joints (Row 1-3 and row 16). The reason for this is unclear at this stage.

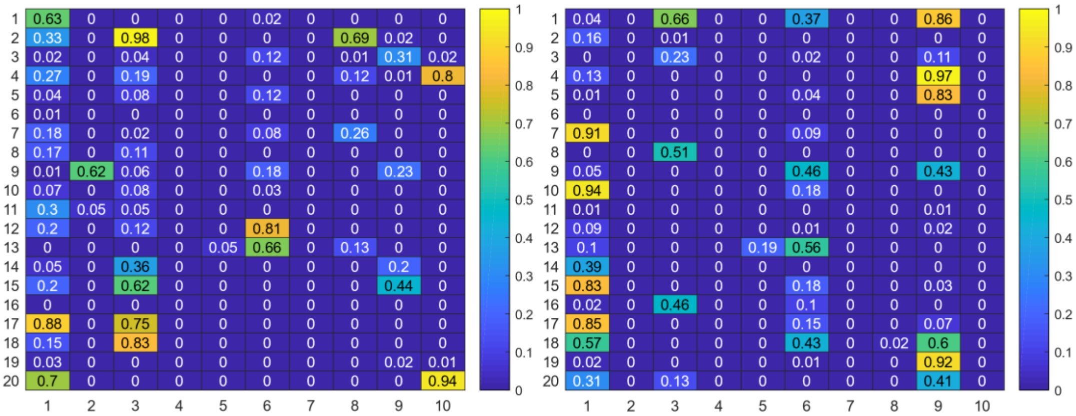
Angles



In the figure above a short example of angles from NN1 test phase (Frames 1:500) are shown. The difference of the magnitude and amplitude of angles as measured with the LM (blue), Vicon (black) or the NN output (red), is instantly visible. The NN further sometimes moves further away from the target Vicon data compared to the LM, which was hypothesised to have worse agreement with the Vicon curves (for example Middle MCP joint FE or Thumb TMJ AA and FE). For other joints the NN prediction shows good agreement. At this stage, the reasons for the various responses of the NN cannot be explained. Possibly the amplitude of joint angles poses a challenge to the neural network, however, and the reasons could be more fundamental and associated with difficulty to measure thumb movements with either mean. The limited agreement between angle curves supports the finding of generally weak correlations.

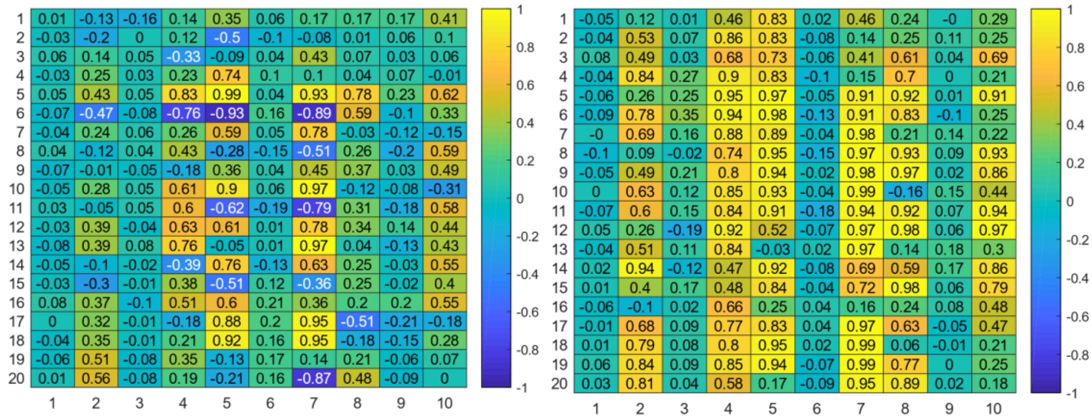
Right hand:

p-value:



On the left, the p-value for the input (LM) to target (Vicon) correlation is shown and on the right the p-value for the NN output to Vicon correlation. There are 40 and 35 insignificant correlations respectively. In comparison to abduction-adduction and flexion-extension movements there are many more insignificant correlations, but it this finding is an accordance with the left-hand thumb circumduction. When assessing the thumb joint specifically (Flexion-Extension angles of the TM (row 1), MCP (row 2) and IP (row 3) joints), still several non-significant correlations can be identified. This contrasts findings from the flexion-extension and abduction-adduction applications, but is in agreement with findings from the left-hand thumb circumduction data.

Correlation coefficient (R^2):



On the left, the correlation coefficient (R^2) for the input (LM) and target (Vicon) correlation (mean R value: 0.13) is shown and on the right R^2 for the NN output to Vicon correlation (mean R value: 0.40). For both approaches' correlations are mostly very weak to moderate, which is in conjunction with the findings in the p-value table. The NN seems to mostly reduce negative correlations but not weak to moderate ones, such as seen in the first data block (x-axis, 1)

RMSE

	1	2	3	4	5	6	7	8	9	10
1	72.5	72.8	66.2	62	65	75	72	71.8	64.1	66.2
2	18.4	16.6	8.4	15.8	12.8	13.7	10.4	10.7	9.3	14.4
3	29.2	27.8	34	19.8	15.7	25.7	29.2	29	15.9	25.1
4	35.1	42.6	49.8	44.6	41	39.5	45.1	49	39.2	38.5
5	18.4	15.5	23.5	23.9	25.7	26.6	22.7	19.7	17.9	18.9
6	17.2	24.2	28.9	17.3	21.5	38.3	26.8	19.9	11.5	15.2
7	37.1	36.2	44.9	39.6	33	34.7	40.3	44.6	43.1	40.4
8	18.4	14.6	21.7	20.3	18.2	2.9	19.6	23	4.8	15.3
9	19.5	24.6	29.2	24.3	25.1	29.2	27	25	15.3	19.3
10	35.8	31.8	41.3	38.6	33.7	39.2	39.5	41.8	44.6	39.9
11	24.9	17.6	23.9	21.7	19.8	4.6	22.4	26.1	7.5	21.3
12	18.6	18.6	18.2	18.4	20.6	18.4	18	16	2.6	15.3
13	41.3	29.9	39.4	30.1	21.1	35.5	37.5	39.3	33.2	39.7
14	28.4	21.1	22	12.8	10.6	18	21.1	21.8	19.9	28.1
15	19.3	20.4	26.4	27.7	27.8	18.6	22.4	23.2	10	16.9
16	16.9	14.9	20.9	12.1	8.2	15.9	11.6	14.3	14	14.5
17	12.1	21.4	16.1	23.3	26.9	18.9	19.4	18.7	8.5	11.6
18	12.5	27.5	14.8	22.5	29.5	31.4	22.9	16	14.1	13.3
19	12.1	23.4	17.8	23.4	31.5	38.3	26.6	17	12	12.8
20	7.4	27.1	21.6	23.5	29.5	36.1	25.9	18.7	9.3	8.3

	1	2	3	4	5	6	7	8	9	10
1	19.5	16.4	10.8	9.9	6.9	8.5	8.2	9.8	8.4	14.1
2	20.1	12.8	9.5	6.1	7.1	7.9	8.4	9.3	7.8	13.7
3	13.8	16.5	13.5	6.2	6.7	7.8	6.1	6.9	9.1	8
4	5.9	11.9	8.8	4.6	3.9	5.4	4.8	3.7	8.5	5.8
5	3.6	11.1	8	3	1.6	1.8	1.6	1.6	2.7	3.4
6	4.5	5.2	5.4	2.8	1.8	2.3	1.7	2.2	4.5	3.8
7	5.1	15.6	8.9	3.6	6.5	3.9	4.8	3.8	7.8	6.6
8	4.9	11	8.1	3.2	2.8	2.4	2.2	3	4.2	5.3
9	3.2	4.3	3	1.3	1.2	0.8	0.6	1.3	2.8	3.5
10	4.9	19	9	3.8	6.9	3.4	4.7	3.9	6.5	6.6
11	6.5	13.4	11.7	4.8	3.3	2.9	2.7	3.5	4.5	6.2
12	4.9	6.3	5.6	2	2	2	1.1	1.2	2.7	3.6
13	8.5	28.6	15.2	9	10.5	5	5.6	6.2	11.6	11.4
14	6.5	7.5	4.1	5.5	4.8	3.2	1.9	2	4.9	7.5
15	2.8	9.4	3.2	2.5	3	2.3	1.4	1.2	2.7	4
16	15.6	16.4	14.9	11.2	9.7	12.2	10.5	10.3	11.4	14.8
17	3.7	9.8	8.5	4.1	8.1	3.1	4.5	5.7	4.7	5
18	3.3	13.4	8.2	4.2	8.4	3.3	4.3	4.8	5.4	4.3
19	3	7.4	8	3	7.9	4	4.1	4.5	4.6	4.5
20	3.8	10.2	7.3	4.7	7.2	3.9	3.1	3.8	2.5	3.1

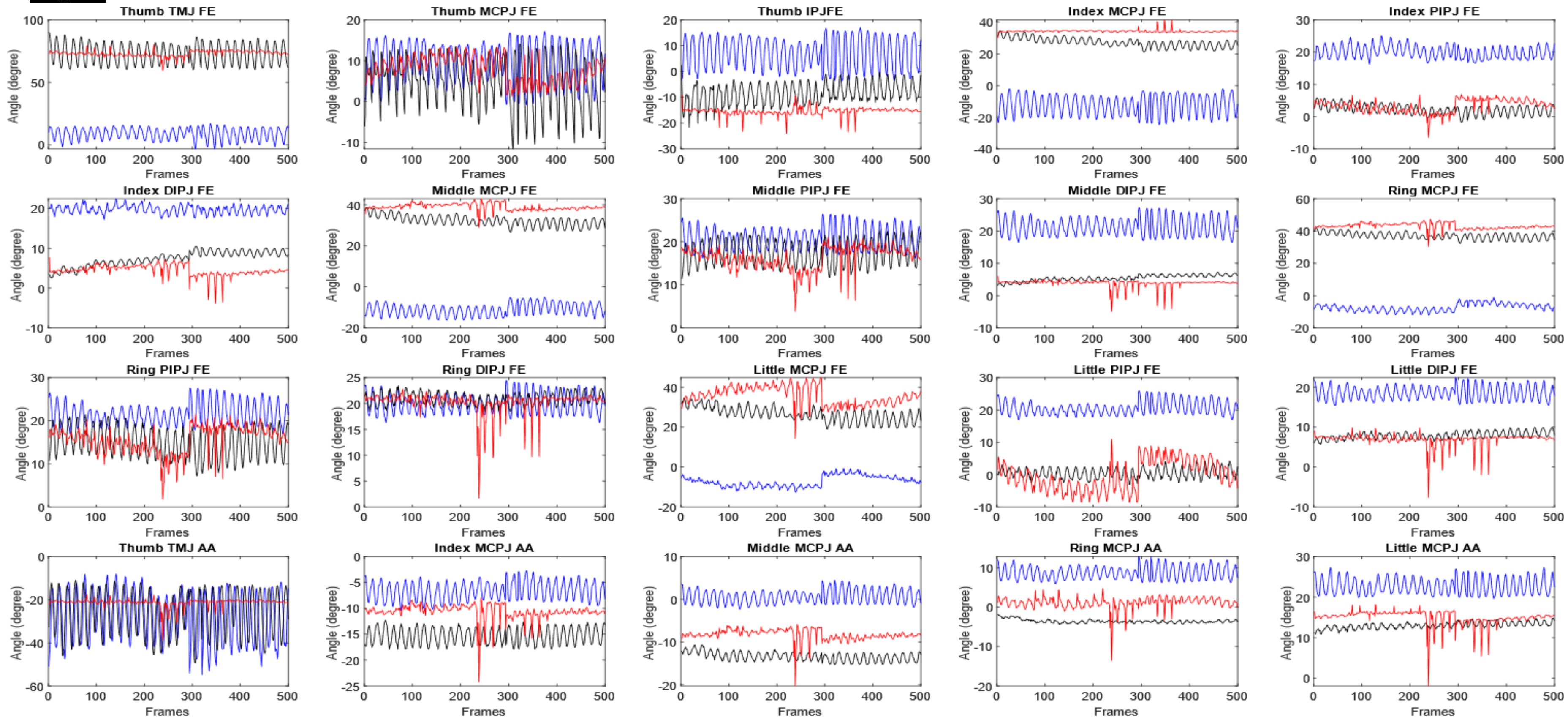
On the left, the RMSE between the input (LM) and target (Vicon) data is shown and, on the right, the RMSE between the NN output Vicon data. The LM-Vicon comparison showed greater RMSE values (Mean: 25.85° ± 14.09°, Range: 2.61°- 75.05°) than the NN output -Vicon comparison (Mean: 6.39° ± 4.31°, Range: 0.65°- 28.60°). On average, the neural network reduces the error of the LM. Interestingly, in this data set, the LM shows greatest differences to the Vicon data for any FE angle of the most proximal joint of each finger (Row 1: Thumb TM joint, Row 3: Index MCP joint, Row 7: Middle MCP joint, Row 10: Ring MCP joint and row 13: little MCP joint). Large errors at the thumb joints, despite being the primarily moving fingers, agrees with findings from the left hand.

Percentage change RMSE

	1	2	3	4	5	6	7	8	9	10
1	-73	-77.5	-83.7	-84.1	-89.4	-88.7	-88.7	-86.3	-87	-78.7
2	9.1	-22.8	12.3	-61.3	-44.2	-42.1	-19.6	-12.9	-16.6	-5.1
3	-52.7	-40.9	-60.2	-68.6	-57.5	-69.7	-79	-76.3	-42.8	-68.1
4	-83.3	-72.2	-82.3	-89.8	-90.4	-86.4	-89.3	-92.5	-78.2	-84.8
5	-80.4	-28.3	-65.9	-87.6	-93.7	-93.2	-92.8	-92	-84.9	-81.9
6	-73.9	-78.7	-81.5	-83.9	-91.5	-94	-93.8	-88.8	-60.7	-74.7
7	-86.4	-56.8	-80.2	-90.8	-80.2	-88.9	-88	-91.6	-82	-83.7
8	-73.3	-24.2	-62.8	-84	-84.4	-15.8	-88.7	-87	-11.6	-65.5
9	-83.6	-82.3	-89.7	-94.8	-95.2	-97.1	-97.6	-94.9	-81.5	-82
10	-86.4	-40.2	-78.2	-90.3	-79.6	-91.2	-88.1	-90.6	-85.5	-83.4
11	-73.8	-24	-51.2	-77.9	-83.5	-36.7	-88	-86.7	-40.3	-70.8
12	-73.9	-66.2	-69.2	-88.9	-90.1	-89.2	-93.9	-92.8	4.7	-76.4
13	-79.5	-4.4	-61.5	-70	-50	-85.9	-85	-84.3	-65	-71.3
14	-76.9	-64.6	-81.4	-56.8	-54.7	-82.2	-91.1	-90.7	-75.2	-73.3
15	-85.5	-53.7	-87.7	-91.1	-89.2	-87.4	-93.7	-94.7	-72.8	-76
16	-8	10	-28.7	-7.9	18.6	-22.9	-9.4	-28.1	-19	2.6
17	-69.3	-54.2	-47.1	-82.6	-70	-83.6	-76.6	-69.6	-44.6	-56.8
18	-73.9	-51.3	-44.6	-81.5	-71.6	-89.5	-81.3	-70.1	-61.9	-67.8
19	-75.2	-68.3	-55.3	-87	-75	-89.7	-84.4	-73.3	-61.7	-65.1
20	-48.2	-62.3	-66	-80.1	-75.7	-89.2	-88.2	-79.7	-72.8	-62.6

The percentage change in RMSE between the two methods (LM to Vicon and NN output to Vicon) was calculated. As the purpose of the NN method was to reduce the error of the LM, a negative value in the table indicates a reduced RMSE value. And positive value indicates an increased RMSE after for the NN output data relative to the LM raw data. On average the RMSE was reduced by 75%, which was found to be significant ($p<0.001$). Whilst reduced on average, in several 10% data sets the RMSE for the thumb joints (row 1-3 and row 16) increases following the application of the neural network, which cannot be explained at this stage.

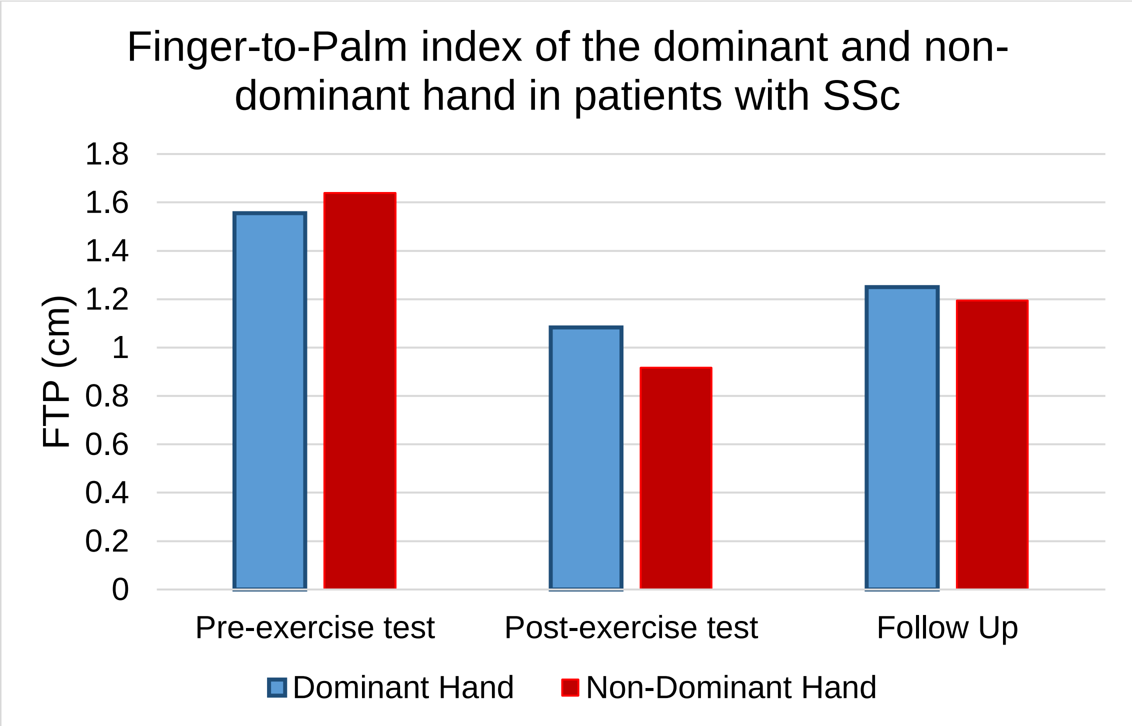
Angles



In the figure above a short example of angles from NN1 test phase (Frames 1:500) are shown for the LM (blue), Vicon (black) and NN prediction (red). With changing agreement between the respective curves, the NN prediction shows errors at around 50% of the curve despite unchanged patterns in the original target (Vicon) and input (LM) data. It is therefore challenging to determine a cause for this error in the prediction of the NN. The limited agreement between angle curves supports the finding of generally weak correlations and is in agreement with findings from the left hand. In general thumb circumduction was poorly predicted compared to the angles predicted during flexion-extension and abduction-adduction movements.

Appendix 6:

Only the dominant hand was evaluated when examining the effectiveness of the intervention protocols in Chapter 7. This decision was made as there was no statistically significant difference of range of motion in the dominant and non-dominant hand as measured with the Finger-to-Palm index (FTP) in patients with SSc. To ensure accuracy this comparison was repeated at all three test sessions, yet the pattern remained the same and no statistical difference, as determined by a paired samples t-test) was identified at any stage between the dominant and non-dominant hand. Prior to the exercises the average FTP was slightly higher on the non-dominant hand ($p = 0.72$), whereas at the post-exercise and follow up test the FTP of the non-dominant hand was slightly less ($p = 0.11$ and $p = 0.71$ respectively).



Appendix 7:

Is that a Vicon in your pocket? An evaluation of the Leap Motion capturing finger movements

Elena Eusterwiemann[1], Marina Anderson[2], Mark A Robinson[1], Gabor J Barton[1]

[1]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK.
[2]Department of Rheumatology, Aintree University Hospitals NHS Foundation Trust, Liverpool, UK.

Introduction: The Leap Motion controller is a markerless, portable method for capturing hand and finger movements. It accurately and precisely registers positions of finger tips under static and dynamic conditions [1,2] and computes joint angles between finger bones. Yet, the accuracy of the angle computation is unknown in comparison to a gold standard optoelectronic system. The aim of this study was to compare angles measured with the Leap Motion controller and a Vicon system and assess if an artificial neural network can predict true finger movements from joint positions calculated by the Leap Motion device.

Methods: A Leap Motion sensor (£49.99) was positioned under a hand to capture 3D coordinates of the carpometacarpal, metacarpophalangeal (MCPJ), proximal interphalangeal (PIPJ), distal interphalangeal (DIPJ) joints and the fingertip. Joint coordinates were streamed into D-Flow (Motek Forcelink, Amsterdam) via its Network module using a custom made C# program. 3D coordinates of retro-reflective markers dorsal to the CMCJ, MCPJ, PIPJ and DIPJ joint centre and Tip were streamed simultaneously from Vicon (16MX cameras, Vicon Nexus 2.5) into D-Flow. Data of five flexion/extension cycles (8.3 s) was sampled at 300Hz. Joint angles were computed between two adjacent segments and the offset was removed by subtracting the mean LMC angle from the Vicon angle [3]. Following principal component analysis of the marker coordinates, a backpropagation neural network (Matlab Neural Network Toolbox) was trained with 75% of the decorrelated principal scores to estimate the nonlinear function between the Leap Motion and Vicon. The remaining data were used to test the function with unseen data. Three 3D models of the finger were created in Visual3D (Leap Motion, Neural Net, Vicon). The root mean square errors (RMSE) of joint angles were calculated between the Leap Motion and Vicon, and the Neural Net estimation and Vicon.

Results: The raw differences of the angles between Leap Motion and Vicon ranged from 1.96° to 34.54° reducing to an RMSE of 3.44° to 15.43° after offset correction. The RMSE between angles of the Neural Net estimation and Vicon were 1.7°, 2.4° and 1.9° in the MCPJ (Figure 1), PIPJ and DIPJ respectively.

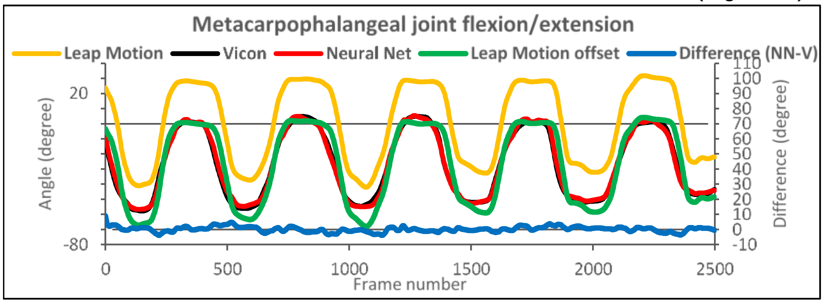


***Figure 1:** Left Index finger MCPJ angles from Leap Motion, with offset correction, Vicon, and Neural Net.*

Discussion and Conclusion: Raw data angles measured by the Leap Motion controller are not sufficiently close to a gold standard optoelectronic system, but an offset correction improves this error. A close match with a Vicon system was achieved by appropriate pre-processing and function estimation with an artificial neural network. The large difference between the Leap Motion and Vicon finger model is due to the Leap Motion reconstructing joints from the video image of the palmar surface while the Vicon markers are on the dorsal side and that the Leap Motion calculated joint positions based on an algorithm. Future research will compare angle profiles from the Leap Motion controller to data acquired using a validated six-degrees-of-freedom model.

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Appendix 8:

Abstract for The British Society of Rheumatology Annual Conference 2017

Title: Development of a virtual rehabilitation game for scleroderma: gender differences in unimpaired controls

Author: Elena Eusterwiemann[1], Marina Anderson[2], Mark Robinson[1], Gabor Barton[1]

[1]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK

[2]Department of Rheumatology, Aintree University Hospitals NHS Foundation Trust, Liverpool, UK

Abstract:

Objective:

Hand mobility impairments due to scleroderma have a large impact on activities of daily living ultimately leading to reduced quality of life. Restoring hand mobility is crucial to maintain mental and physical well-being but adherence to rehabilitation programmes is low. A motivating and interactive rehabilitation approach specific to scleroderma is needed. We aimed to 1) develop a smart game for improving finger extension and 2) compare finger movements and gaming performance of males and females with normal hand function to inform game training of patients with scleroderma.

Methods:

We created and tested an interactive, virtual rehabilitation game (FlappyBall) to evaluate finger mobility in 24 young healthy adults (12 males: 24.7yrs±2.3 and 12 females: 24.8yrs±2.8). A Vicon motion capture system and single marker on a finger nail was used to measure finger extension range of motion to drive the game which involved directing a ball through an obstacle course: the ball would fall if the finger was within 80% of its range of motion, and rise if the finger was in the final 20% of its range of extension. Duration of game play was used as a measure of performance. A complex 3D hand model of 28 markers was also used to assess angles and angular velocities in each joint. A correlation analysis was performed to determine if gender or kinematic movement characteristics relate to game performance, which would impact the intervention duration or design of future applications to be used with patients.

Results: Males performed significantly better at the game than females ($P=0.025$) in spite of no gender differences in the magnitudes of finger angles and angular velocities. The kinematic movement profiles of fingers were not related to game performance (all $P>0.05$) which varied greatly, in particular among male participants. Performance initially improved but declined after ten consecutive trials for both genders, yet all performance changes were found to be insignificant ($P>0.05$).

Conclusion: Finger kinematics could not explain the differences in game performance between males and females, suggesting differences in motor control. Males have a more effective control of voluntary finger extension in response to cognitive stimuli, which might be linked to higher exposure levels to video games, or greater degree of hand-eye coordination. Despite the game play being perceived as fun and stimulating, the difficulty needs to be matched to individual levels of ability, respecting gender differences, to prevent frustration and reduced motivation. Further, the performance decline after ten trials suggests that breaks are needed to allow a short mental and physical recovery phase to prevent fatigue. We are now aiming to develop a portable biofeedback game that specifically targets commonly experienced movement limitations of scleroderma patients, determined by a functional three dimensional movement assessment.

Appendix 9:

Gait & Posture 65 (2018) 7–8

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Short communication

O 004 - Motion capture without markers using the leap motion controller and artificial neural networks

E. Eusterwiemann[a,*], M.A. Robinson[a], M. Anderson[b], G.J. Barton[a]

[a] Liverpool John Moores University, Faculty of Sciences-School of Sport and Exercise Sciences, Liverpool, United Kingdom
[b] Aintree University Hospital, Department of Rheumatology, Liverpool, United Kingdom

ARTICLE INFO

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Markerless motion capture
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Leap motion
Vicon
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1. Introduction

The Leap Motion controller (LM) can reconstruct joint centres and a hand skeleton in real-time without the need of markers. Compared to a gold-standard optoelectronic system, the LM is inaccurate when calculating angles between two adjacent finger segments [1]. Artificial neural networks (NN) learn multi-dimensional patterns between two data sets and after training can predict output data based on input data presented to it.

2. Research question

Can an artificial Neural Network improve the accuracy of angles calculated from Leap Motion data?

3. Methods

Two young, healthy adults were fitted with 16 clusters (48 markers) on the dorsum of the hand and each phalanx. Markers were captured with 15 Vicon cameras (Vicon Nexus 2.5). The LM was placed ~25 cm underneath the hand and captured 3D finger joint (carpometacarpal, metacarpophalangeal, proximal interphalangeal (PIPJ), distal interphalangeal) and tip coordinates. The systems were synced and 15 cycles of self-selected hand movements were collected in D-Flow at 300 Hz (Motek Forcelink, Amsterdam). Vicon marker data was imported into Visual3D (C-Motion) where functional joint centres were computed (GILETTE algorithm). The first 8 principle components of LM and Vicon data (explaining 97.6% of data variance) were used to train a back-propagation NN in Matlab including 10 fold-cross validation. After training, the NN performance was tested with previously unseen test data set (10% of all data). Computed and predicted joint centre locations were correlated. Joint angles were calculated in Matlab using the cosine rule, for LM, Vicon computed and NN predicted joint centres. The RMSE was calculated between Vicon and NN joint centres as well as joint angles.

4. Results

Correlation coefficients (R) between 0.94–0.99 were calculated between computed and predicted functional joint centres (Fig. 1) across the 10-fold validation ($r2 = 0.89–0.99$). The RMSE between computed and predicted joint centre locations ranged from 0.13 mm to 2.05 mm (mean: 0.55 mm). RMSE increased from proximal to distal end of each finger. The RMSE between Vicon joint angles and NN predicted joint angles at the Index PIPJ (Fig. 2) was 6.45°, compared to 12.54° between the LM and Vicon data, reflecting an error reduction of 48.56% when the NN was applied.

5. Discussion

The neural network was able to improve the accuracy of the LM as shown by the angle error reduction between NN and Vicon, compared

* Corresponding author.
E-mail address: K.E.Eusterwiemann@2015.ljmu.ac.uk (E. Eusterwiemann).

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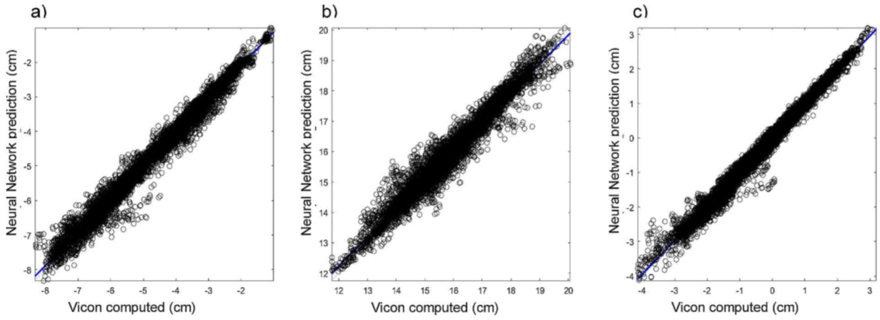

Fig. 1. Correlation between Vicon computed (X-axis) and Neural (Y-Axis) network predicted joint centre coordinates. Strength of the correlation was assessed by calculating the correlation coefficient (R) and coefficient of determination (r^2). a) Correlation of joint centre X coordinates ($R = 0.98953$, $r^2 = 0.9792$) b) correlation of joint centre Y coordinates ($R = 0.97689$, $r^2 = 0.9543$) c) correlation of centre Z coordinates ($R = 0.99238$, $r^2 = 0.9848$).

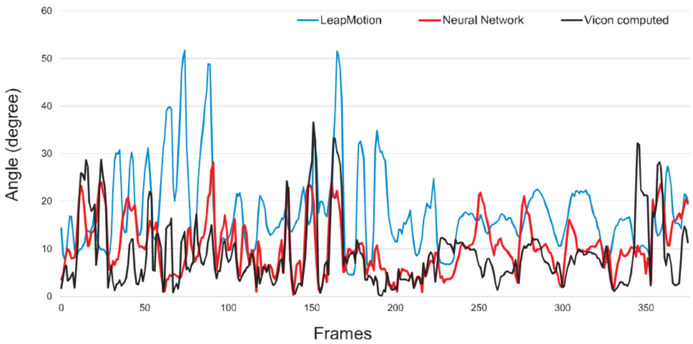

Fig. 2. Flexion/Extension angles at the Proximal Interphalangeal joint from reconstructed test data for the neural network (previously unseen data). Angles (degree) computed using cosine rule for the Leap Motion input data (blue), Vicon target data (black) and Neural Network prediction (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to LM and Vicon. The angles were computed using cosine rule, which is limited if the angle of interest is close to 0°, however, despite this the results are convincing. In future, the LM will be used to assess movement limitations in patients.

References

[1] Eusterwiemann, et al., Is that a Vicon in your pocket? An evaluation of the leap motion capturing finger movements, CMAS Annual Meeting, Salford, UK, 2017.

Appendix 10:

Improved accuracy of markerless finger tracking with the Leap Motion, using an artificial neural network

Elena Eusterwiemann[1], Gabor J Barton[1], Mark A Robinson[1], Marina Anderson[2]

[1]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK.
[2]Department of Rheumatology, Aintree University Hospitals NHS Foundation Trust, Liverpool, UK.

Introduction

The Leap Motion, a device developed for touchless computer interaction, can reconstruct joint centres and a hand skeleton in real-time, and thus offering a solution to markerless hand motion capture. Compared to a gold-standard optoelectronic system, the Leap Motion is inaccurate when calculating joint angles between two adjacent finger segments [1]. Root mean square error (RMSE) for joint flexion/extension angles ranged from 3.44° to 15.45° after offset correction. In motion capture, markers are applied to track segments used to calculate joint angles, making accurate marker tracking essential to determine angular motion correctly. Artificial neural networks (NN) are able to learn multi-dimensional patterns between two data sets, input and target outcome, during a training phase [2]. After successful training, an artificial NN is able to predict outcome data based on input data presented to it. Neural networks were successfully applied to predict EMG patterns to improve the use of EMG-controlled prosthetic arms and hands [3]. The aim of this study was to evaluate if an artificial NN can improve the accuracy of the Leap Motion.

Research Question

Can the Leap Motion, in association with artificial Neural Networks, be used for accurate markerless 3D motion capture?

Methods

Following institutional ethical approval, nine young, healthy adults were fitted with a retro-reflective marker setup (48 markers) arranged in 16 rigid clusters with three markers each. Clusters were placed on the dorsum of the hand in the middle of each phalanx, and the palm. Marker coordinates, captured with a Vicon system (15 T160 and T10 MX cameras, Vicon Nexus 2.5), were streamed live into D-Flow (Version 3.26.0, Motek Forcelink, Amsterdam). The Leap Motion (£50) was placed ~25cm underneath the hand and captured 3D finger joint (carpometacarpal, metacarpophalangeal, proximal interphalangeal, distal interphalangeal) and tip coordinates, relative to the device. Joint coordinates were streamed live into D-Flow via its Network module using a custom-made C# program. Participants performed 15 cycles (25s per cycle) of self-selected hand movements, which were captured simultaneously by the Leap Motion and Vicon in D-Flow at 300 Hz. Principal component analysis (PCA) was performed on Vicon markers and Leap Motion joint coordinates. The first 20 principle components (explaining 99.97% of data variance) were used to train a backpropagation NN (Matlab Neural Network Toolbox) with the Bayesian regularisation algorithm using 20 input, 20 hidden and 20 output neurons. The decorrelated principle scores were randomly partitioned into training (80%), validation (10%) and test sets (10%). During training, the NN gradually developed a non-linear, multivariate function between Leap Motion joint centres and Vicon marker coordinates. Training terminated when the NN performance gradient dropped below the defined minimum value ($1e^{-7}$). The NN function was tested with the previously unseen test data set. Reverse PCA was performed on the NN output to obtain predicted 3D marker positions. The relationship and error between captured Vicon and NN generated marker coordinates was assed using linear regression analysis and RMSE.

Results

Regression analysis between Vicon measured and NN predicted marker positions gave a correlation coefficient (R) of 0.9994 (r^2= 0.9988). The RMSE between marker coordinates from Vicon and the NN prediction was calculated in 2 steps: First the RMSE for each marker and dimension was calculated separately. Secondly, the mean RMSE_XYZ of one marker was calculated, providing a single RMSE value for each marker reflecting three dimensions. The RMSE values ranged from 0.182mm to 0.43mm, and an average RMSE for all 48 markers of 0.278mm.

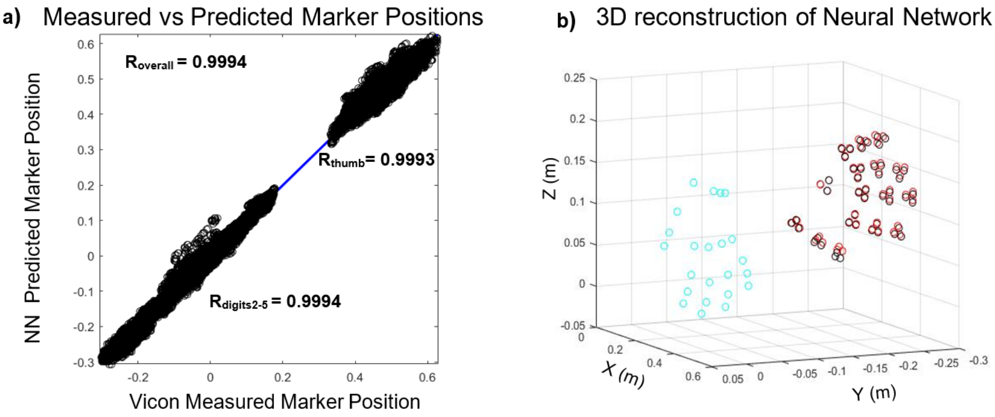

Figure 1: a) Test phase Vicon Marker data plotted against NN reconstructed Marker positions. The data samples around the optimum correlation gradient (blue, slope = 1). The thumb is separated (top right corner) from the remaining fingers due to anatomical structure. b) 3D reconstruction of the Neural network Leap Motion inputs (blue), Vicon Targets (red) and neural network marker position prediction (black) for a single test frame.

Discussion

A large agreement between measured Vicon and NN predicted marker positions was identified. With sufficient training the NN is able to predict marker coordinates from Leap Motion data with high accuracy, thus the Leap Motion can potentially be used as a device for markerless 3D motion tracking. These results cannot be directly compared to angles measured in degrees [1]. However, the NN improves the accuracy of the Leap Motion as angular calculation with precisely reconstructed markers reconstructed will be close to Vicon angles. In future we will test this principle to predict joint centres and movement patterns from Leap Motion data in a cohort of healthy controls and patients with hand movement impairments.

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Appendix 11:

QUANTIFYING HAND MOVEMENT LIMITATIONS IN SCLERODERMA DURING FUNCTIONAL TASKS USING THE MOVEMENT DEVIATION PROFILE

E. Eusterwiemann[1], M. A. Robinson[1], M. Anderson[2], G. J. Barton[1]
[1]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom
[2]Department of Rheumatology, Aintree University Hospital, Liverpool, United Kingdom
Email: k.e.eusterwiemann@2015.ljmu.ac.uk

Summary

Disease-induced impaired hand function relates to reduced quality of life, and is frequently assessed by physicians in routine care of scleroderma patients. Hand movements are complex and current clinical assessment are objective or inaccurate. A mixed cohort of scleroderma patients and healthy controls performed two functional tasks and the finger-to-palm index. Joint angles of the frontal and sagittal plane were calculated and analysed using the movement deviation profile (MDP). Results showed significant deviations from normality in scleroderma patients during functional tasks. While some significant correlations between movement deviation and clinical measures were identified, no clinical measure correlated to deviation of both functional tasks, suggesting that one clinical measure is insufficient to assess hand impairments in scleroderma patients.

Introduction

Scleroderma, a rare rheumatic autoimmune disease, increases the stiffness and thickness of connective tissues, leading to flexion contractures at the hands. Impaired hand function is associated with a decline in quality of life and mental health [1], and therefore needs to be frequently assessed in clinical practice. Current clinical assessments subjectively rank patient perception of difficulty to perform activities of daily living or inaccurately quantify finger flexion range. The movement deviation profile (MDP) is a single curve describing the distance between abnormal patient movement and typical healthy movement [2]. This study aimed to quantify hand movement deviations from normality of scleroderma patients during functional tasks and to compare MDP results to simple clinical measures.

Methods

Five patients (62.4 ± 15.1, all right-handed females) and eleven healthy controls (55.9 ±14.7yrs, 9 females, 2 males, all right-handed) performed two functional tasks: opening a 1) large lid and 2) zipper from a standardised seated position. The Finger-to-Palm Index (FTP) [2] was taken for all participants prior to placing 48 markers on the dorsum of the hand. Movements were captured in Vicon Nexus 2.5 using 15 Vicon MX cameras (Vicon Inc., Oxford). Joint angles were calculated in Visual3D (C-Motion) for the sagittal and frontal plane. Movement deviation from normality of each patient was determined using the MDP. Age, years since diagnosis, movement duration (from onset of movement to grasp completion) and maximum extension angles were correlated to the mean MDP. Pearson's correlation coefficient (r) was tested for significance and the coefficient of determination (r^2) was calculated. An independent sample t-test was performed between healthy control and patient data for 1) movement duration and 2) maximum extension angle.

Results and Discussion

All patients showed variable, but statistically significant deviations from normality during both functional tasks. Almost all patients required significantly more time ($p<0.05$) to perform both functional tasks. Mean movement deviation correlated to clinical and movement parameters revealed two significant correlations: 1) Movement deviation when opening a zip significantly correlates to FTP ($p = 0.043$) and 2) Movement deviation when opening a lid correlated to movement duration ($p = 0.0021$) (Table 1). Strength of correlation (R^2) is however only weak to moderate.

Conclusions

Movement deviations only correlated to the FTP only for the zip task, but not when opening a lid. The FTP measures finger flexion ability, which is essential for grasping small objects, such as zips. When opening a large lid, the movement requires a larger extension range, and less flexion, which could explain the lack of correlation for the lid task. The data indicates a trend of correlation between MDP and maximum extension angle for the lid task. Therefore, a maximum extension test chould be included routine in clinical assessment. No tested parameter correlated to the MDP for both functional tasks, suggesting that movement deviation from normality is task-specific and cannot be addressed with one single measure.

References

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Table 1: Movement Deviation Profile (MDP) correlations with 1) Finger to Palm Index (FTP), 2) Years since diagnosis (Disease duration), 3) Mean Maximum extension angle (mean of all maximum extension angles) and 4) Time to perform the functional task (Movement time)

	MDP to FTP			MDP to Disease duration			MDP to max. extension angle			MDP to Movement time		
	Pearson r	p-value	R^2	Pearson r	p-value	R^2	Pearson r	p-value	R^2	Pearson r	p-value	R^2
Lid	0.3112	0.2788	0.0968	-0.0819	0.7807	0.0067	0.4316	0.1234	0.1862	0.7478	0.0021	0.5592
Zip	0.5837	0.0463	0.3407	0.3808	0.2219	0.145	-0.0975	0.763	0.0095	0.0328	0.9195	0.0011

Appendix 12:

Comparing the effectiveness of virtual rehabilitation and physiotherapy on finger mobility and ability to perform ADL in scleroderma patients

Elena Eusterwiemann[1], Mark A Robinson[1], Marina Anderson[2], Gabor J Barton[1]

[1]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK.
[2]Department of Rheumatology, Aintree University Hospitals NHS Foundation Trust, Liverpool, UK.

Introduction

Scleroderma triggers an autoimmune response, leading to increased fibrosis and collagen production, often resulting in reduced mobility of the wrist and fingers. Patients with scleroderma commonly struggle to perform activities of daily living (ADL) and rely on help from others or specially adapted utensils[1,2]. Hand exercises, based on passive stretches, which are thought to be beneficial for tense tissues, are recommended. Adherence to such physiotherapy is low and mixed results are reported regarding the effectiveness[2]. Virtual rehabilitation has the potential to increase motivation and adherence to exercise using an active range of hand and finger motion combined with a high number of repetitions. The aim of this study was to compare the effects of virtual rehabilitation and physiotherapy on finger mobility and ability to perform ADL.

Research Question

Can virtual rehabilitation and physiotherapy improve finger joint range of motion and ability to perform ADL in scleroderma patients over four weeks?

Methods

Six patients (all female, white British, 53.1±10.6 years) were recruited from a local hospital and split into two equal groups. One group followed a non-supervised physiotherapy programme based on hand stretches and squeezing tasks. The virtual rehabilitation group played a custom-made computer game aiming to improve range and agility of flexion-extension movements as well as abduction-adduction movements at the metacarpo-phalangeal joints. A 3D motion analysis using the LeapMotion controller (LeapMotion Inc.) to calculate range of motion at each joint, and validated questionnaires (Cochin Hand Function Scale (CHFS) and Michigan Hand Outcomes Questionnaire MHOQ_ADL)) were conducted before and after completion of the training programme. The change in range of motion (ΔROM) of the dominant and non-dominant hand, CHFS (ΔCHFS) and MHOQ_ADL (ΔMHOQ_ADL) were tested for significance using a one-way mixed ANOVA (Matlab, Mathworks).

Results

Mean ΔROM varied among the participants and individual joints. Both groups showed improvements on all parameters before and after the training (Figure 1a). The ANOVA analysis showed a significant effect of the group for ΔCHFS ($p=0.04$) and dominant hand ΔROM ($p=0.01$) (Figure 1b), but not for the non-dominant hand ΔROM (0.79) or the ΔMHQ_ADL outcome (dominant hand: $p=0.25$, non-dominant hand: 0.45).

Discussion

Questionnaires revealed significant improvements in functionality for the virtual rehabilitation group, but not the physiotherapy group. However, the mean change in range of motion was found non-significant, suggesting that factors other than range of motion are contributing to the reduced ability to perform tasks of daily living in scleroderma patients. The virtual rehabilitation group showed greater increases in range of motion, suggesting a more beneficial effect compared to physiotherapy. The exercises were only continued for four weeks, limiting the ability to draw conclusions regarding long-term effects and adherence. Future research should examine the long-term effects of virtual rehabilitation in scleroderma.

<u>References</u>

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a)

	Dominant Hand ΔROM (°) ± SD	Non-Dominant Hand ΔROM (°) ± SD	ΔCHFS score ± SD	Dominant Hand ΔMHOQ_ ADL score ± SD	Non-Dominant Hand ΔMHOQ_ ADL score ± SD
Physio-therapy	0.6 ± 0.9	0.8± 2.7	3 ± 4	9.8 ± 3.5	9.9 ± 7.4
Virtual Rehab-iliation	3.3 ± 2.9	0.9 ± 0.2	15 ± 6.1 *	16.1 ± 7.3 *	15.5± 7.9 *

b)

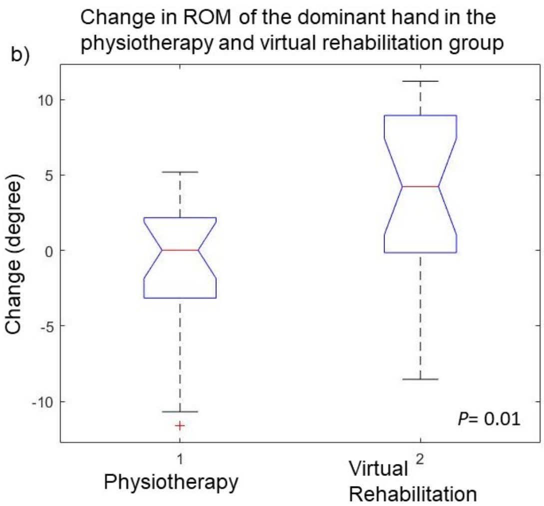

Figure 1: a) Shown is the change (Δ) for range of motion (ROM), Cochin Hand Function Sclae (CHFS) and Michigan Hand Outcome Questionnaire_Activities of Daily living score (MHOQ_ADL) and the respective standard deviation (SD) . Significant within group improvements (marked *) were found in the Virtual Rehabilitation group for all questionnaires. b) Change in range of motion between the groups was found significant in an ANOVA analysis.

Appendix 13:

ABSTRACT NUMBER: 2600

'If You Don't Use It, You Lose It': Rehabilitation of Finger Dexterity and Ability to Perform Activities of Daily Living in Systemic Sclerosis

Elena Eusterwiemann[1], Marina Anderson [2], Mark Robinson [1] and Gabor Barton [1], [1]Liverpool John Moores University, Liverpool, United Kingdom, [2]Aintree University Hospital, Liverpool

Meeting: 2019 ACR/ARP Annual Meeting

Keywords: Biomechanics, Hand function and exercise, Rehabilitation, Systemic sclerosis

SESSION INFORMATION

Date: Tuesday, November 12, 2019

Session Title: Systemic Sclerosis & Related Disorders – Clinical Poster III

Session Type: Poster Session (Tuesday)

Session Time: 9:00AM-11:00AM

Background/Purpose: Hand involvement due to increased skin thickness and skin collagen content is one of the first manifestations of systemic sclerosis (SSc) leading to a reduced joint mobility, flexion contractures and an reduced ability to perform activities of daily living (ADL) (Young et al., 2016). However, successful execution of ADLs not only relies on hand mobility, but also finger dexterity (Perez-Marmol et al., 2017). The activation of small muscles to synchronise hand and finger movement during ADLs is under neural control and reduced use of muscles leads to inefficient recruitment of motor units, and therefore reduced motor skills. Recommended hand exercises for SSc (Young et al., 2016) train range of motion, but less so dexterity. Virtual rehabilitation programmes have shown beneficial effects on both range and motor control (Levin et al., 2015). The aim of this study was to compare the effect of physiotherapy and virtual rehabilitation on finger dexterity and ability to perform ADLs.

Methods: Twenty SSc patients were recruited from a rheumatology clinic (mean age: 54.8yrs± 23.1yrs; female: n=19, male = 1) and randomly split into two groups (each n= 9, drop out: n =2) performing 90min of hand exercises per week for four weeks. One group followed a novel virtual rehabilitation programme, involving playing a computer game using hand movements. The second group completed a physiotherapy exercise regime. Prior to, immediately after and four weeks after completion of the exercises patients filled in the Cochin Hand Function Scale (CHFS). A finger dexterity test on a customised keyboard was completed using digits 2-4 and the average tapping speed over 15 seconds was calculated. A two-way mixed design ANOVA for the CHFS and finger dexterity test was conducted in SPSS and the change in CHFS and dexterity were correlated using bivariate two-tailed Pearson correlation.

Results: Both interventions showed significant improvements in ability to perform ADLs (Figure 1) (p = 0.03) and finger dexterity (Figure 2) (p = 0.02) when comparing pre-training and post-training tests. Whilst finger dexterity was maintained over the 4-week wash out period (post-training to 4-Week follow up), the ability to perform ADLs was not sustained in the virtual rehabilitation group (p = 0.05). No intervention programme showed a significantly better improvement than the other group on either outcome measure (p = 0.401). Change in CHFS and finger dexterity between test sessions was not correlated (r = -0.09, p= 0.72). This pattern was identical in the non-dominant hand, showing there is no effect of hand dominance.

Figure 2: Cochin Hand Function scale -CHFS- score was significantly reduced after exercises -*significant change in CHFS between pre-training and post-training test-. In the Physiotherapy group, this was maintained after the four week wash out period -** significant reduced CHFS score between pre-training and 4 Week Follow up-. The virtual rehabilitation group showed a loss in hand function after the four week follow up resulting in a non-significant difference between pre-training and 4 week follow up test, but a significant increase between post-training and 4 week follow up -***-.

Disclosure: E. Eusterwiemann, None; **M. Anderson**, None; **M. Robinson**, None; **G. Barton**, None.

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