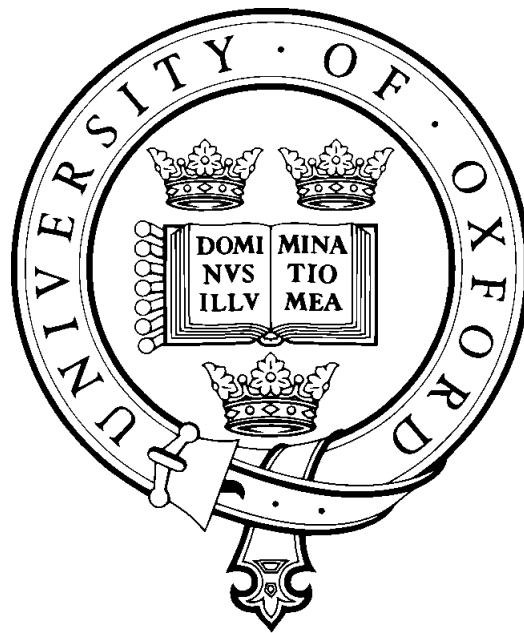


2D Ultrasound elastography as a functional measure of healing of the Achilles tendon *in vivo*



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“The truth would be literally nothing but the shadows of the images.”

Plato

“He that breaks a thing to find out what it is has left the path of wisdom.”

J.R.R. Tolkein

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Abstract

The Achilles tendon is the largest tendon in the human body, which elastically stores and releases energy to facilitate walking and running. Tendons can suffer from a range of pathologies, most notably that of complete rupture, which affects athletes, physically active workers and the aged. There is a growing demand for *in vivo* methods of objectively measuring tendon health for aiding diagnosis, monitoring therapy and for assessment of new treatments. Knowledge of the changes in mechanical properties during the healing process is also limited and new methods to accurately and consistently estimate these could provide insights into the healing process and guide future research efforts.

This thesis presents the development and use of 2D ultrasound elastography, a quantitative strain estimation imaging technique, as a tool to measure changes in the tensile mechanical properties of the Achilles tendon. This technique performs frame-to-frame block matching of image texture to track motion in an ultrasound signal sequence and create a strain estimation field from the spatial derivative of the motion. Elastography in the image-lateral direction of sagittal plane scans is of particular interest as this is in line with the longitudinal axis of the tendon, but presents extra accuracy issues from out of plane motion and lower image spatial resolution. Tendon rupture also presents unique problems to image acquisition and analysis- patient pain and safety are important considerations and disruption of the ultrasound texture can make 2D motion tracking more difficult.

A new 2D elastography block matching algorithm, named ‘AutoQual’, was developed to enable accurate tracking of motion in the image-lateral direction and reduce the impact of artefacts and errors common with damaged Achilles tendons image sequences. It was shown to outperform a multiscale block matching method when tested using ultrasound sequences from *in vivo*, *ex vivo* and gelatine phantom experiments. The input parameters of this algorithm were then optimised using the phantom data for benchmarking.

The AutoQual algorithm was then used to analyse ultrasound sequences from a 24-week longitudinal study of 21 subjects with ruptured Achilles tendons to assess lateral, axial and principal strains during controlled passive motion of the foot or axial palpation of the ultrasound probe. Lateral and principal strains from controlled dorsiflexion were shown to be more repeatable and more sensitive to change than axial strains with manual palpation.

This experience with lateral strain imaging from ruptured Achilles tendons gave an increased knowledge of the strain imaging artefacts and features that can occur. These are described in detail in order that they may be further mitigated in quantitative analysis by optimising acquisition protocols, further amendment of the block tracking algorithm, or exclusion of erroneous areas when selecting regions of interest.

Regularisation is a potential solution to some common artefacts such as discontinuities from poor tracking in shadow regions. Regularisation of the lateral displacement fields is investigated using 2D bicubic smoothing splines. The regularisation parameters used are shown to have minimal effect on quantitative analysis and can aid visual clarity or reduce artefacts within certain settings. However, regularisation was also shown to cause large errors when parameters were set more aggressively.

Finally, it is identified that cumulative lateral strain measurement of the Achilles and other tendons is feasible but that future work is needed to further improve the quality of force and cross sectional area measurements in order to infer mechanical properties accurately. Repeatable high force motion protocols also need to be developed to measure healthy tendons and to ensure comparable results between different patients and research groups.

Publications and Contributions

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Glossary of terms

Calcaneus	-	Heel bone.
Tibia	-	Major bone of the lower leg.
Talus	-	Connecting bone of the foot that provides major rotation pivot for dorsal / plantar flexion.
Achilles tendon	-	Tendon that attaches gastrocnemius and soleus muscle groups to the calcaneus.
Plantaris tendon	-	Tendon connecting the (superficial) plantaris muscle to the calcaneus, sometimes fusing with the Achilles.
Foot/ankle flexion	-	Movement of the foot and ankle in ‘toe lifting’ (dorsiflexion) or ‘toe pointing’ (plantar flexion) motions. The foot rotates about the ankle vertically (when standing) in the sagittal plane.
Scatterers	-	Notionally small particles in tissue that cause an interference pattern in ultrasound pulses and provide tissue appearance texture.
Phantom	-	Artificial model used for ultrasound imaging experiments. In this thesis a porcine gelatine block.
US	-	Ultrasound.
MRI	-	Magnetic resonance imaging.
CT	-	Computer Tomography (imaging).
Lateral	-	The horizontal direction (x-axis) of a US 2D image.
Axial	-	The vertical direction (z-axis) of a US image.
Elevation	-	The notional thickness of a 2D image slice (y-axis).
Block matching	-	Local registration method to establish 1D/2D/3D frame-to-frame displacements.
Elastography	-	Imaging based on strain fields i.e. derived from block matching.
Regularisation	-	Techniques to modify the behaviour of registration techniques to limit unwanted artefacts or unfeasible motion.
Segmentation	-	Delineation and labelling of a tissue or structure in an image.
ABS	-	Automatic Block Size.
QDS	-	Quality Determined Search.
ASR	-	Automatic Search Range.
i SNR	-	Image Signal to Noise Ratio.
NMSE	-	Normalised Mean Square Error.
NCC	-	Normalised Cross Correlation.
SSD	-	Sum of Square Differences.
SAD	-	Sum of Absolute Differences.
F	-	Force.
CSA	-	Cross-Sectional Area.
ε	-	Strain (ratio of extension / original length of material).
σ	-	Stress in mechanical analysis (Force / CSA). Variance in statistical analysis.

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Chapter 1

Introduction

The musculoskeletal system is a complicated structure of hard and soft tissues which function to allow human beings and other vertebrates to interact with their environments; to grip, to lift, to walk and run, for delicate tool use or even for facial expressions and body language. Possession of a healthy set of bones, muscles, ligaments and tendons is a very important factor of people's quality of life.

With a constantly increasing life expectancy across the world, the demand to develop methods to assess the musculoskeletal system is ever-growing. The demand is principally clinical: to accurately diagnose or monitor degenerative conditions; to assess the efficacy of treatments for individuals or for groups; for use in sports for elite athletes and even race horses to assess improvements or deteriorations as part of training. There is also a demand from a biomechanical research perspective: Knowledge of mechanical properties of soft tissues *in vivo* is very limited due to the large variations in species and subjects, the difficulties in handling tissues for mechanical testing and the degradation or changed hydration of tissues *ex vivo*. There is a great amount of difficulty in assessing the properties of tissues and accurate, easy to perform techniques to quantify them *in vivo* could provide a boon of research insights into how materials interact, behave and change.

The whole musculoskeletal system has a diversity of forms, compositions and function. Knowledge of bone properties is relatively well developed due to its solid composition, retention of properties outside of the body and ability to assess via X-ray and computer tomography (CT). Of the soft tissues, muscle is substantially more difficult to assess as it is an active material that can alter its effective stiffness and other properties from voluntary contraction.

This thesis focusses on tendons, particularly the Achilles tendon which attaches the major muscle groups of the lower leg to the foot via the heel. The Achilles was chosen due the availability of data from collaboration with clinical studies, its importance to human ambulation, its large size and relatively simple structure compared with complex tendon

systems like the shoulder rotator cuff. Tendons are passive tissues - their extension or contraction is driven by the external forces on them rather than voluntary action such as in the muscles. The relatively low water content, low vascularity and proximity to the skin makes the Achilles tendon one of the most ideal tissues to study with ultrasound imaging.

Strain measurement from two-dimensional elastography from ultrasound image sequences of passive flexion of the foot is here developed and tested as a tool for tendon health assessment. While 3D ultrasound or magnetic resonance imaging (MRI) are potential imaging modalities to gain great insights, only 2D ultrasound offers a practical compromise on cost, speed of acquisition, frame rate and image resolution factors. The use of 2D imaging means that a significant assumption of planar strain needs to be made. While this does limit analysis, there is a greater wealth of information from investigating a 2D strain field than a 1D analysis.

The main focus is on assessing the complete rupture of the tendon and the healing process. The thesis commences with a background and literature review of the relevant areas of interest from medical, biomechanical and ultrasound imaging fields of research. This establishes the clinical desire for better health measurement of tendons; a little of the important anatomy and known stages of healing; the existing wide variation of findings from the biomechanics literature on *in vivo* properties; the technical background of elastography and some of the alternative technologies that could be considered as potential solutions. In this manner it can be considered as a development project of image-lateral elastography technology for this application, with a series of iterations to develop, benchmark and then look for further improvements at each stage.

Motion and strain estimation in the image-lateral direction of a sagittal plane ultrasound scan (figure 1.1) of a ruptured Achilles tendon offers unique challenges due to lower image resolution than the axial direction, disruption to the tendon due to pathology and shadows from blood clots and surgical suture.

The significant contributions to the field of this thesis are:

- The development of a new 2D ultrasound elastography algorithm designed to cope

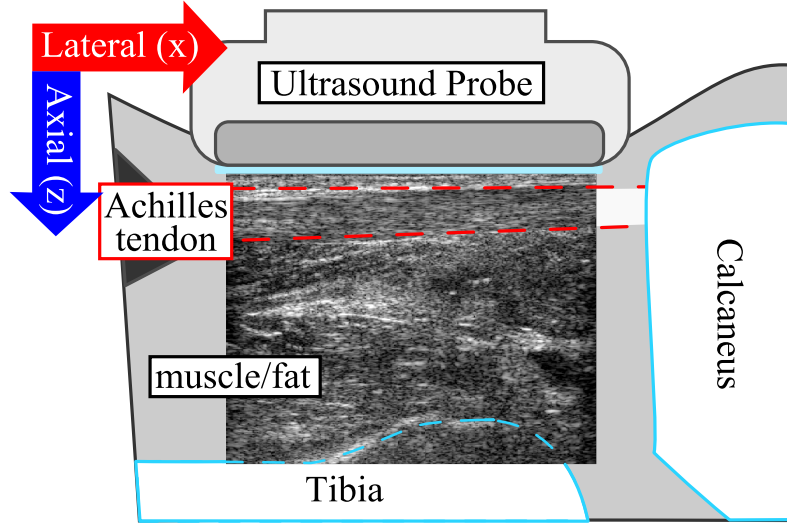


Figure 1.1: *Diagram showing the main features and axis of orientation in a typical sagittal plane ultrasound image of a healthy Achilles tendon. Drawn structures not to scale.*

with the difficulties of lateral elastography in ruptured tendons. This is tested for performance and benchmarked against a previously implemented multiscale elastography method (chapter 4).

- The optimisation of this new algorithm's input parameters to maximise performance (chapter 5).
- The implementation of the new algorithm on a longitudinal study on images of 21 subjects suffering from Achilles tendon rupture. Various parameters derived from the ultrasound image elastography and B-mode images are assessed (chapter 6).
- A detailed description of the nature, cause and mitigation of strain image artefacts found from the experience with rupture patients (chapter 7).
- An investigation of the benefits and risks of regularisation of the strain estimation image using smoothing splines and rejection of outlying errors using synthesized and *in vivo* data (chapter 8).

Chapter 2

Literature review - Medical and Biomechanical

This chapter focuses on the background and motivation for developing new methods for quantitatively assessing the relative health of damaged Achilles tendons *in vivo*. This includes a description of the Achilles tendon, its composition, anatomy, typical pathologies, the healing stages from rupture and existing clinical methods for measuring patient responses to treatment. Biomechanics and simple quantitative strain measurements are introduced and example measurements from *in vivo* studies in contemporary literature are compared and critiqued.

2.1 Tendon structure and substance

Tendons are a vital part of the musculoskeletal system in humans and animals. Used for attaching muscles to bones, they are tough, durable and in many ways rope-like structures which act to transmit the motions from muscle movements to articulate body parts, particularly limbs. In some of the more forceful motions in the limbs, the tendons also elastically store energy to provide more powerful and efficient motion [5,6]. The Achilles tendon is one of these energy storing tendons [1].

Tendon attaches bone-to-muscle tissue and is generally a similar tissue to ligament, the soft tissue that attaches bone-to-bone. Both are tough, strong, fibrous and visually shiny (when seen during surgery) tissues composed of longitudinal fibres. This system of muscles, tendons, ligaments and bone transmits all of the energy used for upright human walking and running. The Achilles tendon is the strongest in the human body, taking an estimated 3.9 times human body weight in load under walking conditions [7] and has been recorded to take up to 12.5 times when running [8]. Even in low energy walking, the elastic storage and release of energy from the Achilles tendon is estimated to contribute approximately 6% of the total work in locomotion. Mechanical energy storage and release become even more important during high energy activities, with nearly 15%

of total energy exerted being shown to be recovered by the Achilles during one legged hopping [9].

This thesis will largely considered tendons as a macro scale material, but it is worth noting that the tissue is actually a highly ordered and complex composite material. There are many levels of fibre hierarchy from fine tropo-collagen material, to sub-fibrils, fibrils, fibres and fascicles which are shown in figure 2.1. This sub-structure helps explain some of the mechanical behaviour of tendon, such as the initial low stiffness to tensile loads being due to elongation of crimped fibres and fibrils (figure 2.2) [10].

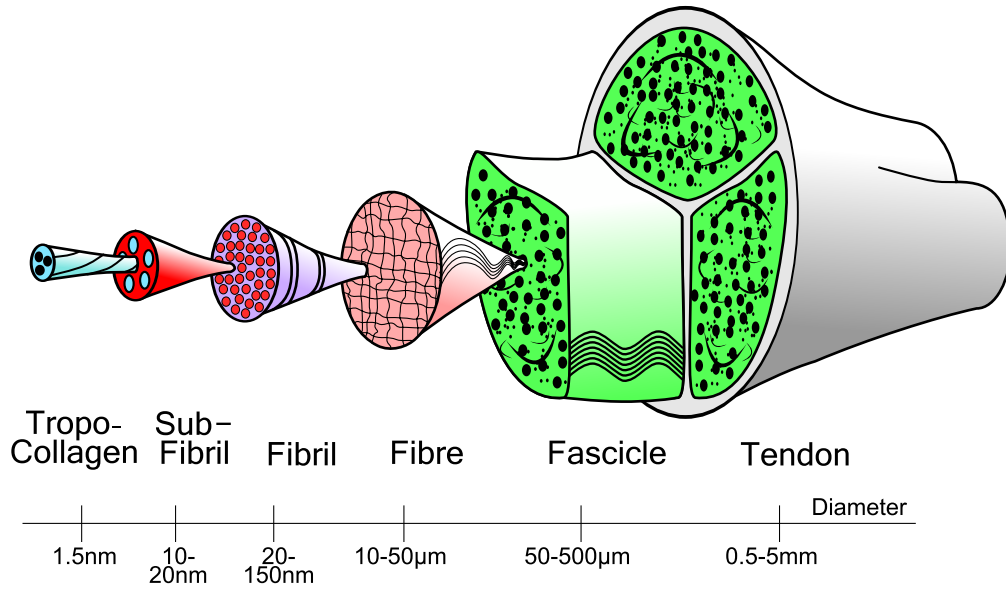


Figure 2.1: Illustration of the organisation of tendon material and typical diameters for healthy tissue. Adapted from Kastelic et al. [11].

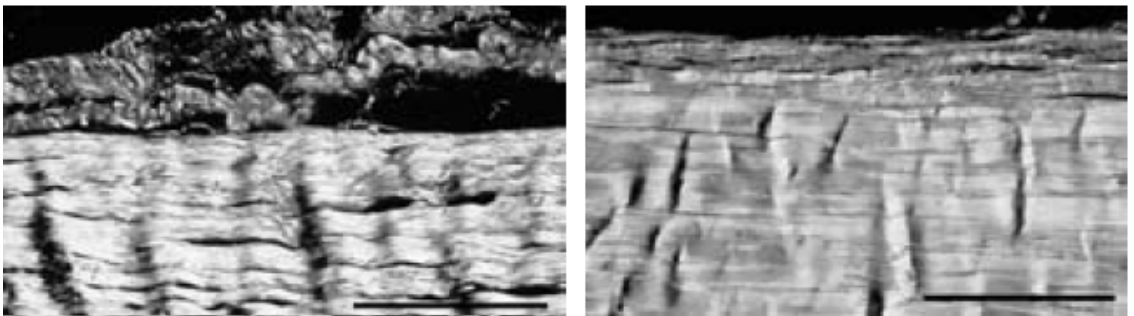


Figure 2.2: Polarised Light Microscopy (PLM) image of fiber crimp in unstrained (left) and prestrained (right) tendon and sheath tissue. Scale bar = 100 μm . Image reproduced from Franchi et al. [12].

The tendon live cells are held in place by an extracellular matrix which is made up principally from collagen fibres (86% by dry weight), elastin fibres (2%), a proteoglycan-water

ground substance containing glycosaminoglycans (GAG) (1-5%) and anorganic components. As with almost all biomaterials, tendon is a dynamic piece of material influenced by chemical reactions and biological control mechanisms [13]. Tenocyte and fibroblast cells are found throughout tendons and are responsible for constantly maintaining, necrotysing and remodelling the tendon structure. The dominant material in tendons is collagen type 1, which forms parallel fibres, with a lesser amount of collagen type 3 which forms more tangled fibres and increases cross linking of the structures [14].

2.2 Achilles tendon anatomy

Although the Achilles tendon is the major load distributor for the muscles of the lower leg and weight of the human body, it is only one part of a larger mechanical system. The main groups of muscles in the area of the Achilles tendon are shown in figures 2.3 and 2.4. Other tendons, ligaments, muscles, fascia and bone will all have some contribution to the loads being taken by the Achilles tendon at any point. The Achilles tendon structure is not trivial as it attaches two major muscles in the leg - the gastrocnemius and soleus - to the calcaneus (heel bone). In some people the plantaris muscle also joins the Achilles prior to insertion [15]. There can be a great deal of variation between individuals, with the (vestigial) plantaris muscle being absent in 7-10% of the population, and the soleus tendon can remain independent until insertion to the calcaneus. The tendinous components of the gastrocnemius can be of 11-26cm in length, the soleus of 3-11cm, and a variable width of the Achilles in healthy adults of 1.5-2.5cm. There is not a clear boundary where tendon turns into muscle, but an intermingling of tendon and muscle fibres, with some tendon fibres continuing quite far into the main part of the muscle. The Achilles tendon is a twisted structure, with fibre rotation spiralling approximately 90° from the point where the soleus tendon starts to contribute fibres to the Achilles and finishing at the bone insertion, with a greater twist in the final 5-6cm [16].

The tendon is encased in a sheath layer called the paratenon, which is made of a fatty tissue that contains the vascular, lymph and nerve supply for the tendon and also serves to allow slip or shear between the tendon and surrounding tissues. Other tendons have 'epitenon' or 'synovial sheath' structures which have slightly different structures and

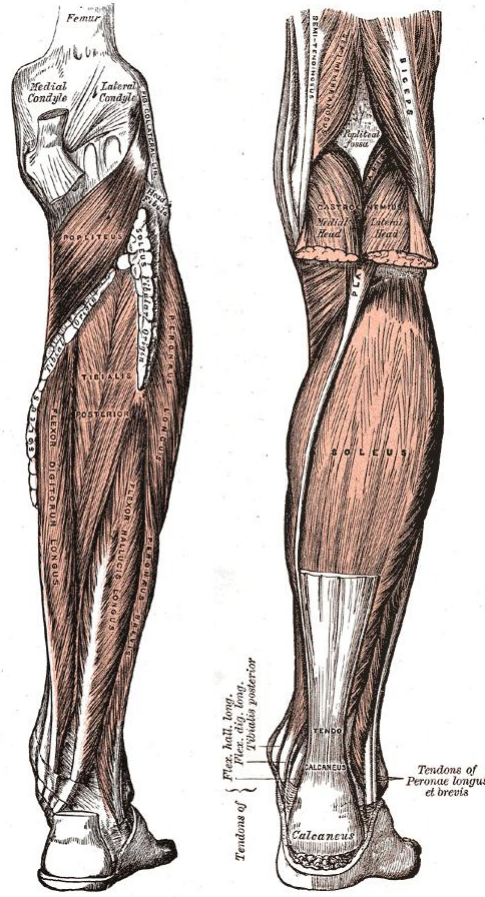


Figure 2.3: *The muscles and tendons at the posterior leg, from Gray's Anatomy [1].*

compositions, but these differences are largely unimportant to the macro-scale mechanical properties of the tendon. The Achilles tendon receives its blood supply via the paratenon as well as the myotendinous junction (MTJ - the join with muscle tissue) and the osseous (bone) insertion. There is an area of decreased blood supply 2-6cm away from the insertion, which is the primary site of Achilles tendon ruptures [16, 17].

There is a watery fat pad and bursa below the tendon that allows substantial volume deformation over the range of foot motion. Forces are transmitted through the Achilles and connected muscles, tendons at the front of the leg and the toes as well as through the bones, principally the tibia in the leg and the talus in the foot. It should be noted that functional motion of the ankle joint is not simple (even in ideal motion there is rotation and translation of bones in multiple axes) and that the multiple muscles, tendons and ligaments of the foot and ankle have to deal with a wide variety of loading conditions to compensate for over balancing or uneven running surfaces and for climbing. This can make detailed mechanical analysis of the loads involved more difficult and often greatly

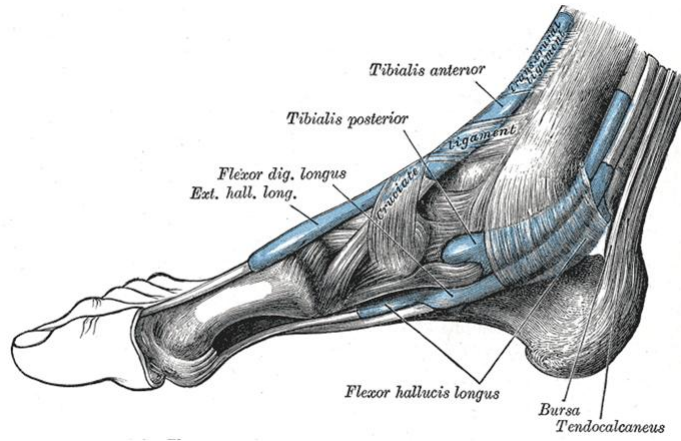


Figure 2.4: *Muscles and tendons of the foot, from Gray’s Anatomy [1].*

simplified models need to be used for analysis of forces. Although a bottom up mechanical analysis is highly dependent upon the activity, studies of relative contributing muscle sizes (where larger diameter muscles are assumed to contribute a proportional amount of force) estimate that approximately two thirds of force are transmitted by the Achilles tendon and connected muscles in active plantar flexion during walking or running [18].

The cross-sectional area (CSA) and shape of the Achilles tendon changes along its length. At the insertion to the calcaneus it is wide and flat, then narrows into the main region while still being of a rounded rectangle in shape. Towards the muscles the tendon eventually bifurcates into the two more circular tendons that connect to the soleus and gastrocnemius muscles. Gao et al. [2] developed a gradient vector flow segmentation of a sequence of 2D ultrasound CSA to determine the change in cross-sectional area of the Achilles tendon *in vivo* along 55mm of its length. They found smooth changes in the CSA as shown in figure 2.5 that correlated well to the tendon thickness measurements, although one dimensional thickness measurements were more prone to variation for any given 2D slice. Aprampatzis et al. [3] found similar maximum and minimum values of CSA from MRI of healthy subjects, but did not get the same profile. This could be due to differences of differentiating tissue types when tendon infiltrates into the muscle in the proximal direction. There is difficulty in the distinguishing tendon tissue from surrounding image texture in ultrasound images as well as some distortion of tissue from the need to compress tissue to maintain acoustic contact *in vivo* which could both substantially contribute error in clinical measurements.

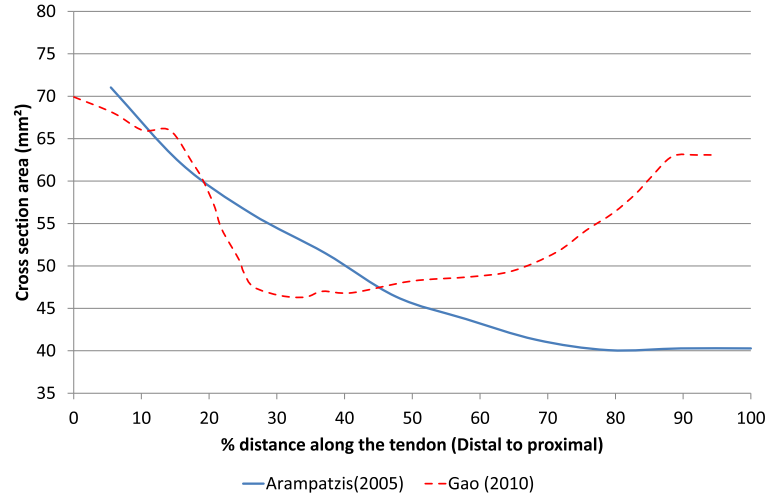


Figure 2.5: *Changes in tendon cross-sectional area (CSA) along its length from insertion [2, 3].*

2.3 Damage and disease

When tendons are damaged, the disruption to motion of limbs is usually very significant. While it is possible to rupture and damage tendon by direct trauma, it is thought that most injuries are related to a chronic degradation of the tendon over a period of time and then a rupture due to an overexertion at the upper end of normal activity. Trauma and disease are, in this case, usually intrinsically linked. The exact causes (etiology) of these degradations are not entirely clear but can be related to overuse, age, microbial action, the reaction to drugs or in diabetes sufferers [19, 20]. It is important to establish a consistent terminology and be clear on the conditions that are of the main interest in this thesis. Various conditions can describe either a fully severed/ruptured tendon, partial rupture or tearing of the tendon, diseases related to surrounding structures or at the interface of tendon to bone (such as inflammation of the calcaneal insertion or of the busra or degradation of the tendon sheath), and diseases that relate to the bulk material of the tendon (tendinopathy, tendinosis or tendinitis). Terminology for tendon disease in the literature is not completely consistent as noted by van Dijk et al. who cite a wide variety and evolution of terminology, particularly in the mid-twentieth century [21].

This thesis mainly focuses on the complete rupture of the tendon as the damage mode and shall describe any prior degradation of the mechanical properties of the tendon as either ‘degradation’ or ‘tendonosis’. This describes a reduction of the tissue material strength with or without any accompanying inflammation, pain or loss of function. Anec-

totally, clinicians have described cases where patients experience pain, but no measurable inflammation or, conversely, a loss of function and clear damage but minimal pain. The terms ‘tendinopathy’ and ‘tendonitis’ are often used to describe conditions with inflammation and pain (respectively) but shall largely be ignored for the sake of clarity here.

The physical appearance of healthy tendon and one with tendinosis is apparent during surgical procedures. Healthy tendon appears ‘glistening white’ and microscope imaging of histology clearly shows the hierarchical parallel bundles of structured collagen fibres with a characteristic reflectance of polarised light. Symptomatic tendons appear grey and more amorphous to the eye, with disrupted and discontinuous collagen-fibre structure visible by microscope and reduced reflection of polarised light. Increased quantities of fibroblast and myofibroblast cells, a lack of inflammatory cells and increased capillary proliferation are all evident. Inflammation lesions are only clear in cases of partial rupture [22].

2.3.1 Stages of healing

There are three main stages in tendon healing: inflammation, proliferation, and remodelling. Ruptured tendons progress through several stages in order to repair to a long-term stable state, as shown in figure 2.6.

In the inflammation stage, various substances are released to the area in the first twenty-four hours, mainly monocytes and macrophages. Vascularity in the tendon and surroundings increases and the synthesis of type 3 collagen begins from tenocytes. After a few days the proliferation stage begins and will last for several weeks. Mechanical signalling becomes more significant from this point, as tendons are able to transmit small loads and this informs the direction of anisotropic repair. The region surrounding the rupture becomes a volume of repairing tissue that is amorphous and mechanically isotropic compared to healthy tendon, with no clear directional linear arrangement. In this stage generation of type 3 collagen is at its highest, with water content and glycosaminoglycan concentrations remaining high compared with an undamaged tendon. The higher water content in part is responsible for a tendon appearing larger in an ultrasound image, even after the tendon scar has formed.

After approximately six weeks, the levels of collagen and glycosaminoglycan synthesis

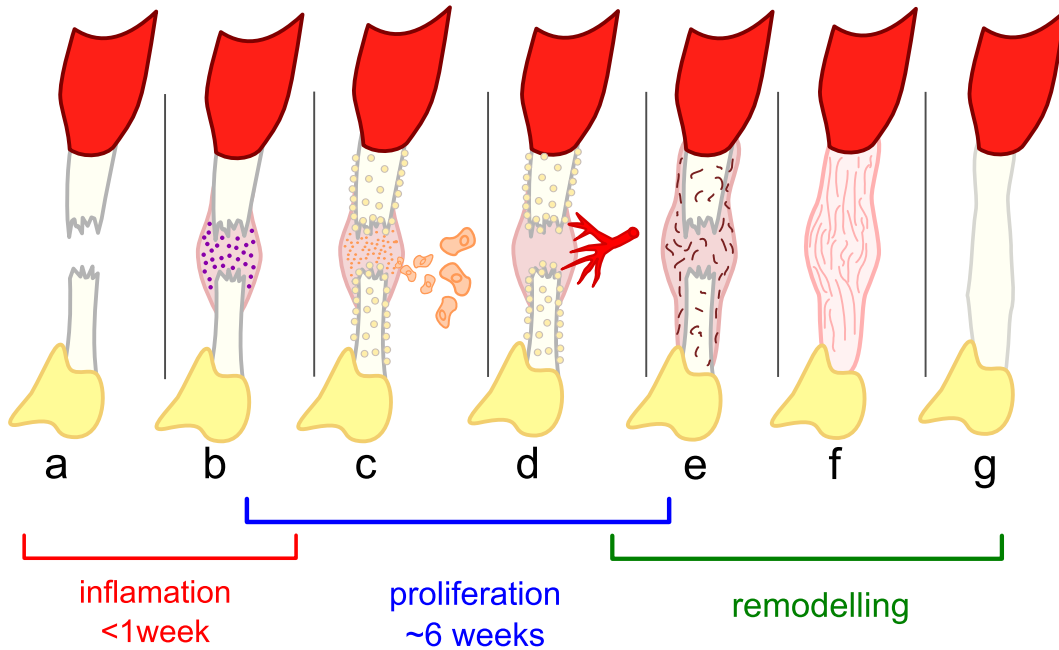


Figure 2.6: *Illustration of tendon repair stages. a: Initial rupture b: Haematoma with platelet activation. c: Invasion of cells and proliferation of paratenon. Production of collagen (mainly type 3). d: Vascular and neuronal ingrowth. e: Loose collagenous callus formation, increased collagen type 1. f: Mechanical stimulation. g: Maturation and remodelling (diagram adapted here from rat Achilles tendon study [23]).*

decrease and the remodelling stage begins. Over the course of a year, the scar tissue becomes trained to the direction of mechanical loading and so becomes more like the original anisotropic tendon material. Vascularity gradually decreases too as the need for improved blood flow diminishes [17]. This healing process has been demonstrated by histology of biopsies from ruptured flexor tendon rat models as shown in figure 2.7 [24].

It has been shown that mechanical loading is important to tendon healing from studies of rat models with artificially ruptured Achilles tendons. Studies have shown that daily loading episodes of otherwise unloaded tendons improves final strength [25], that loading in both the inflammatory and proliferation stages improves final tendon properties [26] and that mild loading increases tissue quality, but heavier loading increases the size of callus [27]. It has been suggested that this may be due to micro-trauma caused by the mechanical loading increasing local biological signaling [28].

A tendon does not actively contract like the muscles it is attached to and so has a much lower energy and oxygen requirement. The oxygen consumption in tendons and ligaments is around 7.5 times lower than in skeletal muscles [17]. Tendons rely much

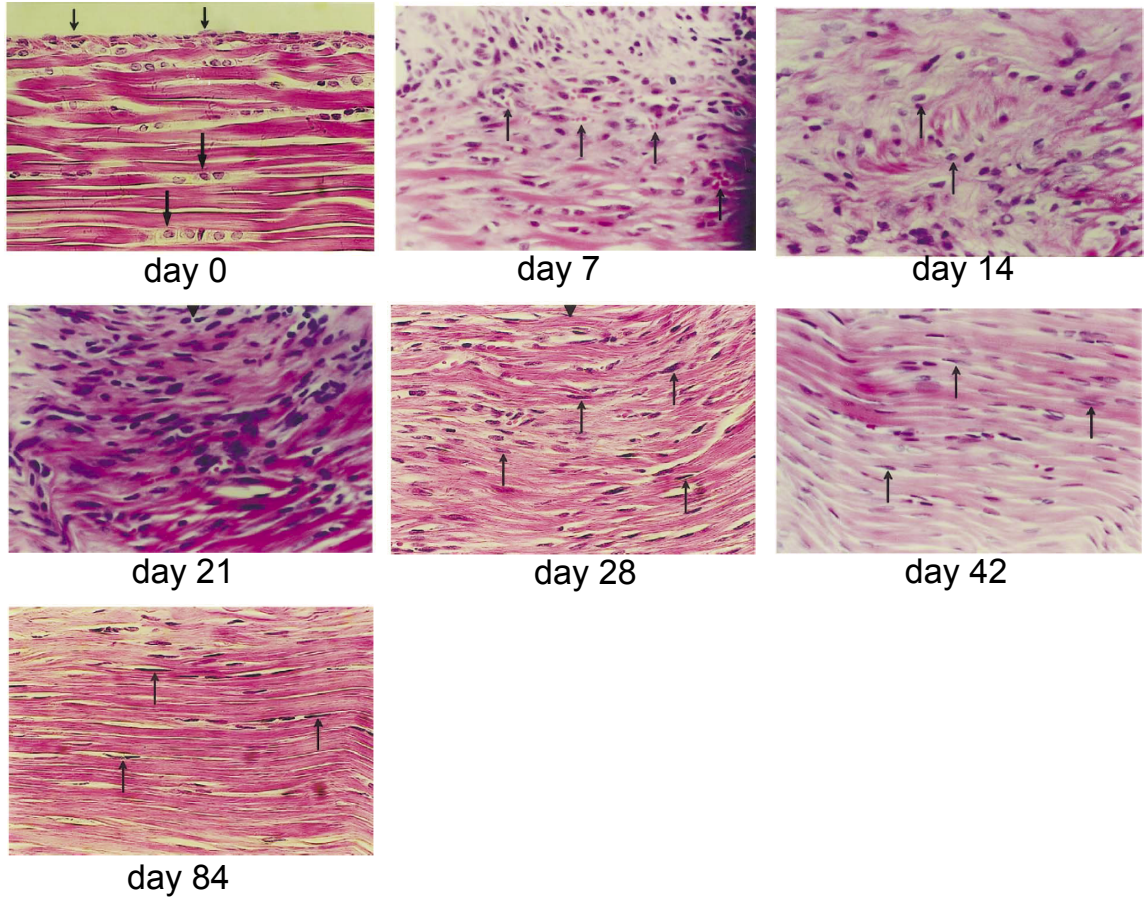


Figure 2.7: *Histology slices of rat flexor tendon with artificial rupture at 400x magnification. **Day 0:** fibroblast cells in epitenon (small arrows) and endotenon (large arrows) with healthy, linear tendon cells. **Day7:** Collagen matrix is degraded into thin fibres, increased endotenon fibroblast cells and new capillary vessels (arrows). **Day14:** New, randomly oriented fine collagen fibres replace previous collagen fibre bundles. **Day 21:** Cells and fine collagen fibres are now longitudinally aligned. **Day 28:** repair site is now completely crossed by parallel fine collagen fibres interspersed with slender cells. **Day 42:** Collagen bundles are now apparent, with endotenon fibroblasts present (arrows). **Day 84:** Collagen Bundles and cellularity now resembles healthy tendon tissue. Images and annotation from [24]).*

more on anaerobic respiration to prevent ischemia when under load. This all enables tendons to maintain a more dense structure and have reduced vascularity compared to many other soft body tissues. Due to low vascularity for the supply of repair substances and the much lower metabolic rates, tendons heal more slowly than other soft tissues. In the Achilles tendon there is a particularly hypovascularity in the zone 2-7 cm proximal to the insertion to the calcaneus (heel bone). This is one of the regions where rupture can be a common occurrence [17].

2.3.2 Treatment

There are few treatments to help improve the speed of recovery or the quality of healing from rupture or damage.

Surgery can improve the healing time by stitching the two ends of the severed tendon together, thus reducing the healing area and the requirement to remodel into a well functioning structure. There is evidence from top level analysis that surgery reduces rerupture rates. Wilkens et al. [29] recorded 667 Achilles tendon rupture patients and found that 3.6% of surgically treated patients reruptured versus 8.8% in conservatively treated. Patient specific analysis is more difficult; Sadoghi et al. [30] attempted to perform a meta-analysis of 11 studies to determine initial mechanical properties of tendons treated with different surgical suture techniques, but found that a lack of consistency in study design and small study sizes made differentiation impossible. Schepull et al. [31] calculated the mechanical modulus of elasticity for Achilles tendons at 7 and 12 weeks post-rupture and determined that those surgically treated were not distinctly different from those which were conservatively treated [32].

Alternative treatments are being researched (and used) to further improve the speed or quality of healing, such as injection of growth factors [33], fetal calf serum, platelet rich plasma [34, 35], dry-needling to induce localised trauma [36], autologous transplantation (autograft) of tissue from other tendons, and the use of artificial scaffolds or patches to encourage cellular growth [37]. These types of methods are assessed by either final strength assessments, histopathology, pain response or function based surveys of groups of patients.

The most popular treatments are forms of activity that are shown to aid ranges of motion, strength and time until return to sport. Concentric (standing on tip-toes) and eccentric (bearing weight on ball of foot with toe-lifting motion performed by stepping backwards down a step) exercises have been proven effective [38] and additional tools to analyse the mechanics of these or alternative activities would be beneficial.

2.4 Requirements for new metrics of tissue healing

Ultrasound elastography is an imaging technique that has the potential to be useful both as an insightful research tool into mechanical properties and to be usable for providing measurements of properties that are related to conditions which could aid clinical practice. The majority of this chapter focuses upon the state of technology in this field; the premise of this thesis is to describe, investigate and further develop this technique. However, it is also worth noting that there are alternative image-based methods being researched to assess the condition of tendons *in vivo*, and that this will aid motivation of elastography within a wider context.

It is also worth noting that, while state of the art attempts to accurately measure the mechanical properties of tendons as a research activity are of interest, there are slightly different requirements for a measurement to be used in clinical practice in order to monitor conditions. These requirements somewhat relax the requirement of accuracy, but emphasise the assumption that the macroscopic mechanical properties are intrinsically linked to tendon health, which has not been indisputably proven. Defined here, a robust metric for clinical use should ideally be:

- **Accurate** - this is a measure of how close to the true physical value that the metric achieves and can be considered as a systematic or offset error. Accuracy should not be over emphasized, as accuracy is secondary to sensitivity to the underlying condition and to precision of measurements. For example, it is possible to have an accurate measure where the mean of a distribution is close to the true value but which is less effective as a clinical metric than one with a narrower spread and a mean offset that can be accounted for by calibration (Figure 2.8).
- **Precise** - repeatability of metrics is important as it raises the chances that any individual measure will be representative of the true value of the metric under consideration. Precision is the element of random error introduced (see figure 2.8) Low precision can be somewhat mitigated by taking multiple measurements and presenting a mean or median value. Doing this improves the confidence that the precision error is minimal. This can assist in group studies to assess the effectiveness

of different treatments but is undesirable as an assessment tool for individuals where patient and clinician time is a premium.

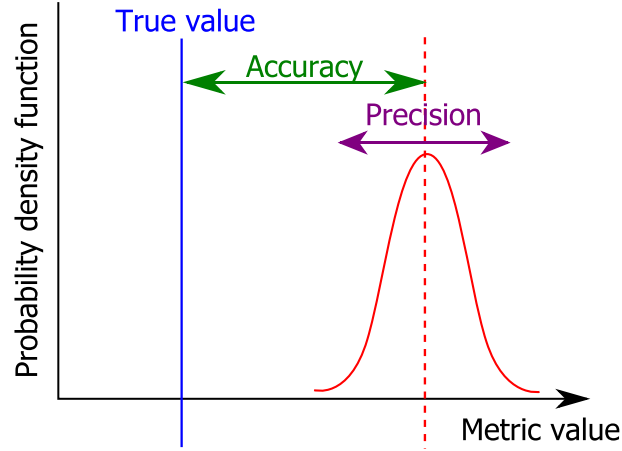


Figure 2.8: Accuracy is defined as a systematic offset error, precision as a random, variable error that affects repeatability.

- **Responsive** - as continuous values are being measured, responsiveness is defined as the amount of difference that is witnessed between different subjects or over time. For instance, a metric may be both repeatable and accurate, but if that value only minimally changes as time progresses or cannot distinguish between different distinct patient groups then the metric is of no benefit.
- **Sensitive** - For a detection-type problem, the measure should successfully detect the pathological state. Sensitivity (or "true positive rate" (TPR)), is the measure of true positives (TP) detections found, divided by the total number of positive detections possible (true positives + false negatives (FN)) or:

$$TPR = \frac{TP}{TP + FN}$$

- **Specific** - this is the antithesis of sensitivity; while the metric should show positive change due to changes in the underlying property it should also not show change where there has been no change. In a diagnostic application, a false positive could lead to unnecessary treatments or changes to athletes training programs which would greatly diminish the value of condition monitoring. Specificity (SPC) is defined as the number of true negative detections divided by the total number of negative

detections possible (false positives (FP) + true negatives(TN)):

$$SPC = \frac{TN}{FP + TN}$$

Sensitivity and specificity are often set by plotting true positive rate against false positive rate on a receiver operating characteristic (ROC) curve. This helps define both the utility of the system and helps set parameter values for detection-type problems. As this report presents continuous measurements and does not directly relate to detection these are not presented.

2.5 Existing clinical measures of Achilles tendon function and healing

Existing clinical methods for assessing healing in Achilles tendons are often not well established, justified or managed. The most commonly used tools are surveys that include a combination of physical measurements and patient questionnaires about subjective pain response. A recent meta-study into patient reported outcome measures used to assess Achilles tendon rupture management by Kearney et al. [39] found that in the 50 research papers investigated there were 21 different outcome measures, 17 of which were *directly* related to Achilles tendon (the remainder being *general* health surveys) and only 4 of which had any evidence to support their validity [39]. These four scores were the Achilles Tendon Total Rupture Score (ATRS) [40], the American Orthopaedic Foot and Ankle Society score (AOFAS) [41], the Leppilahti score [42] and Olerud and Molander Ankle Score (OMAS) [43]. Of these, only ATRS was identified as having been "developed using recognised methodology". An additional score used as a clinical outcome by clinical studies associated with our work (and not referred to by Kearney et al.) is the Victorian Institute of Sport Assessment-Achilles questionnaire (VISA-A) score that has been designed to assess tendinopathy [44]. This score has been assessed using two control groups against two groups of subjects with diagnosed tendinopathy that were treated surgically or conservatively.

For research purposes it is sometimes acceptable to take small core biopsies to measure relative quantities of biological compounds which indicate the rate of progress. This is principally a measure for use in comparing treatment groups in clinical trials or to explore mechanisms of response between different treatments. Tissue is removed from the healing tendon by core biopsy with a diameter of 1-5 mm. Samples are fixed with a solution of formalin, embedded in paraffin and then sectioned into the thickness of a few microns. There are various stains used to improve the contrast of different cellular structures; hematoxylin-eosin staining is common [45–47]. The types and quantities of cell types can be assessed and different stains employed to measure quantities of growth factors.

Biopsies of this type and size are not acceptable as a general monitoring method for clinical practice as the additional trauma caused may impede the healing process or affect the final properties of the healed tendon.

2.6 Biomechanics of Achilles tendons

Mechanical properties are widely thought to be of potential importance as measures of effectiveness and therefore health of energy storing flexor tendons. There are indications that tendinopathy is linked to a degradation of mechanical properties [48]. The ability of muscle-tendon units to store energy elastically rather than just chemically is extremely enabling, allowing for fast and high powered motions such as jumping [49, 50] or throwing as well as improving efficiency of motion, an effect that has been investigated for use in human form robotics [51]. It has also been shown from large histopathology studies of patients that in the majority of cases there is a degradation of tissue structure prior to rupture [52]. It therefore follows that a measure of the properties of these tissues may be a good indicator of their health - provided that there is a good understanding of what a healthy or acceptable response is for the subject.

2.6.1 Stress, strain, stiffness and Young’s modulus

2.6.1.1 3D and 2D material strain

Forces, when applied to a material, cause a deformation. The amount and shape of that deformation will depend upon the force distribution and the material properties. Strain

is a non-dimensional measure of the change in length of a material element with respect to its initial length. For a cubic element, the strains can be described by the differentials of displacements (u, v, w) as tension/compression in the three orthogonal dimension axes (ε_x , ε_y and ε_z), and as shear strains (ε_{xy} , ε_{yx} , ε_{xz} , ε_{zx} , ε_{zy} and ε_{yz}) in each plane (figure 2.9).

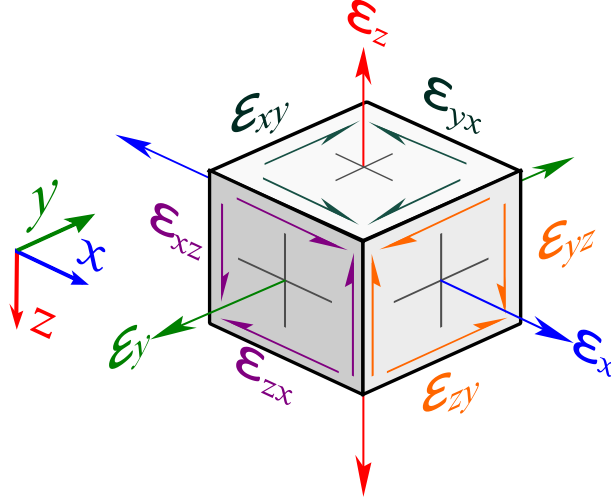


Figure 2.9: Example of a 3D material cube element subjected to linear and shear strains in Cartesian coordinates. For ultrasound images these axes are: x =lateral, z =axial (depth), y =elevation(2D slice thickness).

In this cartesian arrangement, the linear component strains are described by:

$$\varepsilon_x = \frac{\partial u}{\partial x}; \quad \varepsilon_y = \frac{\partial v}{\partial y}; \quad \varepsilon_z = \frac{\partial w}{\partial z} \quad (2.1)$$

and the shear components by:

$$\varepsilon_{xy} = \frac{1}{2} \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right); \quad \varepsilon_{xz} = \frac{1}{2} \left(\frac{\partial u}{\partial z} + \frac{\partial w}{\partial x} \right); \quad \varepsilon_{yz} = \frac{1}{2} \left(\frac{\partial v}{\partial z} + \frac{\partial w}{\partial y} \right) \quad (2.2)$$

There is also reciprocity of the shear strain such that:

$$\varepsilon_{xy} = \varepsilon_{yx}; \quad \varepsilon_{xz} = \varepsilon_{zx}; \quad \varepsilon_{yz} = \varepsilon_{zy} \quad (2.3)$$

This can be conveniently summarised in the 3D strain matrix:

$$\underline{\underline{\varepsilon}} = \begin{bmatrix} \varepsilon_x & \varepsilon_{xy} & \varepsilon_{xz} \\ \varepsilon_{yx} & \varepsilon_y & \varepsilon_{yz} \\ \varepsilon_{zx} & \varepsilon_{zy} & \varepsilon_z \end{bmatrix} \quad (2.4)$$

As the axes are arbitrary relative to the material, they can be rotated to any orientation (see figure 2.10 for 2D illustration) to generate a new strain. A simple rotation could aid assessment of true strain values in a test piece if there is a discrepancy between the force direction and the observation angle.

In fact there is always an orientation for an infinitesimal element where the shear components are zero. In this orientation the remaining orthogonal strains are known as ‘principal strains’. These 3D principal strains ($\underline{\underline{\varepsilon_p}}$) can be found as the Eigen-values of the strain matrix (equation 2.5) and the angles from the original axes to the re-oriented principal axes from the Eigen-vectors.

$$\underline{\underline{\varepsilon_p}} = \begin{bmatrix} \varepsilon_{p1} & 0 & 0 \\ 0 & \varepsilon_{p2} & 0 \\ 0 & 0 & \varepsilon_{p3} \end{bmatrix} \quad (2.5)$$

There are special cases, where the material is a thin plate (one set of element faces is stress free) or the strain is dominated by one or two dimensions, strain can be assumed to be *planar*. In these instances, the matrix in equation 2.4 can be reduced to:

$$\underline{\underline{\varepsilon_p}} = \begin{bmatrix} \varepsilon_x & \varepsilon_{xy} & 0 \\ \varepsilon_{yx} & \varepsilon_y & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad (2.6)$$

Planar strain could be used as an approximation for tissue tensile strain. However, making the assumption of planar strain will fail to capture some of the behaviour of a real tendon and may induce additional quantitative errors due to out of plane motion.

In systems where it is unclear that the local stress direction in the tissue is in line with the supposed system axis, it may increase the accuracy or measure responsiveness to change to measure the maximum 2D principal strain. As previously mentioned, the

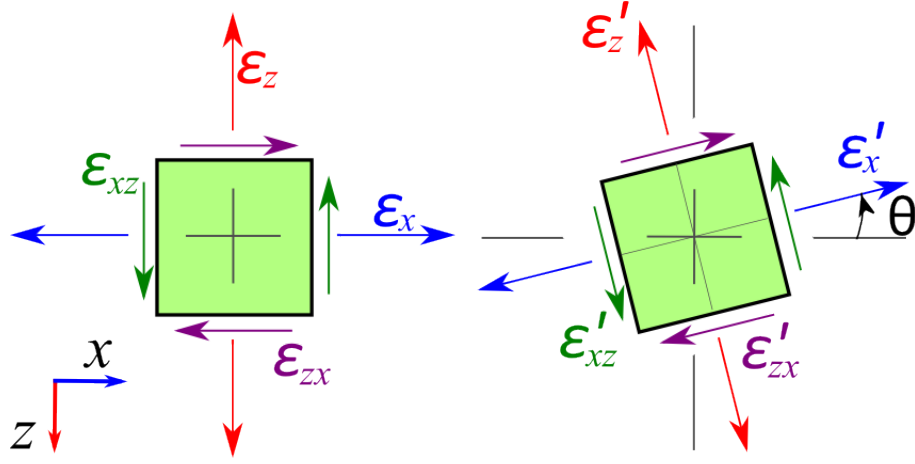


Figure 2.10: *Demonstration that the image coordinates can be arbitrarily rotated by angle θ , to obtain the principal strains and maximum/minimum shear strains.*

imaging axes are arbitrary and can be rotated by angle θ to find a new 2D strain according to these new axes (x', y' , $x'y'$ in figure 2.10 and equation 2.7).

$$\begin{aligned}\varepsilon_{x'} &= \frac{\varepsilon_x + \varepsilon_y}{2} + \frac{\varepsilon_x - \varepsilon_y}{2} \cos 2\theta + \varepsilon_{xy} \sin 2\theta \\ \varepsilon_{y'} &= \frac{\varepsilon_x + \varepsilon_y}{2} + \frac{\varepsilon_x - \varepsilon_y}{2} \cos 2\theta - \varepsilon_{xy} \sin 2\theta \\ \varepsilon_{x'y'} &= \frac{\varepsilon_x - \varepsilon_y}{2} \sin 2\theta + \varepsilon_{xy} \cos 2\theta\end{aligned}\quad (2.7)$$

Assuming small strains and small shear rotations ($\frac{\partial u}{\partial x} \ll 1$, $\frac{\partial w}{\partial z} \ll 1$, $\varepsilon_{xz} \ll 1$) the maximum and minimum principal strains can be found by trigonometry as:

$$\varepsilon_x = \frac{\partial u}{\partial x} ; \varepsilon_z = \frac{\partial w}{\partial z} ; \varepsilon_{xy} = \frac{1}{2} \left(\frac{\partial u}{\partial z} + \frac{\partial w}{\partial x} \right) \quad (2.8)$$

$$\varepsilon_{p1,p2} = \frac{\varepsilon_x + \varepsilon_z}{2} \pm \sqrt{\left(\frac{\varepsilon_x - \varepsilon_z}{2} \right)^2 + \varepsilon_{xy}^2} \quad (2.9)$$

2.6.1.2 Relating strain to stiffness and Young's modulus

Stiffness is a potentially useful quantity for measuring in a tensile elastic structure such as the Achilles tendon. Stiffness is the measure of how much force is required to stretch or compress a material. For a one dimensional linear elastic material (figure 2.11) the tensile extension or compression will change according to Hooke's law (equation 2.10).¹

¹Note that more complex models (notably Voigt, Maxwell and Kelvin standard linear solid [53, 54] models) are used to account for viscoelastic behaviour as well as the use of fractional

The simplest analysis possible for assessing stiffness in the tendon would be a one dimensional and linearly elastic system (figure 2.11 and equation 2.10). Here, the extension of the material in one dimension is assumed to be proportional to the force exerted on it. This is an even greater assumption than the 2D case and does not capture any shear behaviour within the tissue.

$$F = kx \quad (2.10)$$

Where F is the force applied, x is the extension from the neutral position and k is the elastic stiffness.

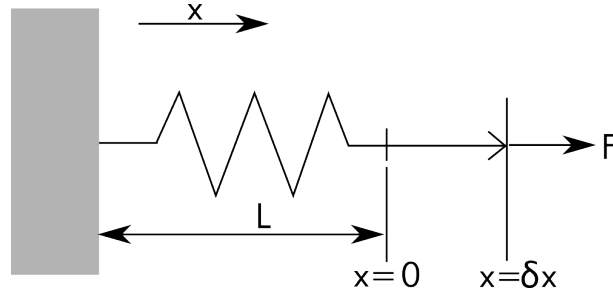


Figure 2.11: *Example of a simple linear mechanical model for a linearly elastic material.*

This requires extension for the general case where the material may not be linearly elastic. As a property of interest for Achilles tendon function, it is useful to think of stiffness as relating how much energy can be stored per unit extension as described by equation 2.11.

$$U = \int F.dx \quad (2.11)$$

where U is the total energy stored (J), F is the force applied (N) and x is the elongation (mm). Graphically this describes the area under a force-extension curve. For the general case, the stiffness of a material is defined as the gradient of the force extension graph at any one point as shown in equation 2.12.

$$U = \int \int \frac{dF}{dx}.dx^2 \quad (2.12)$$

For a linearly elastic material the force gradient (stiffness) is constant as shown in equation calculus [55, 56].

2.13.

$$U = \int \int k \cdot dx^2 = \int kx \cdot dx = \frac{1}{2}kx^2 \quad (2.13)$$

In this way it can be seen that the stiffness of a material is the ability of it to store recoverable energy per unit extension squared. Of itself this is not necessarily a measure of health in an Achilles tendon, as differences in genetic disposition or life circumstances may lead to variation. There may also be benefits to less stiff tissue to reduce the chances of high-impact forces which lead to tearing along the tendon's length or in the attached muscle. However, if monitored over time or compared to the subject's other Achilles tendon (assuming it to be healthy) it may be possible to use stiffness as a measure of patient specific health.

The stiffness itself is not a material property though, as it is dependent on the thickness and initial length of the specimen (which likely change much between subjects) as well as the tissue composition. These can be normalised out to find the specimen's Young's modulus - a measure of the material's energy density (energy per unit volume) as a function of extension. This is usually expressed simply as the stress (force per unit area) divided by the strain (extension per unit length) over the linear extension region as shown in equation 2.14.

$$E = \frac{\sigma}{\epsilon} = \frac{F/A_0}{\Delta x/L_0} = \frac{FL_0}{\Delta x A_0} \quad (2.14)$$

For the non-linear case this must be defined by the gradient as shown in equation 2.15 and its instantaneous value will depend upon where in the strain range it is measured.

$$E = \frac{d\sigma}{d\epsilon} = \frac{d(F/A_0)}{d(x/L_0)} = \frac{L_0}{A_0} \frac{dF}{dx} \quad (2.15)$$

These conventional definitions of elasticity work well for purely elastic materials, and there are more property interdependencies when the material is homogeneous and isotropic. Unfortunately, tendon tissue is certainly not isotropic (due to its linear hierarchical structure).

Tendon is also believed to be a viscoelastic material, which exhibits both properties of elasticity (where elongation is resisted and the original length is recoverable) and viscosity

(resistance shear flow and strain as a function of time). At the molecular level, the elastic elements represent the stretching of chemical bonds and the viscous elements to the diffusion of molecules or slipping of fibres within the material. The principal consequences of this are that viscoelastic materials will creep (elongate) when subjected to a constant stress, and that hysteresis will occur under cyclic loading releasing heat and decreasing efficiency.

2.6.2 *In vivo* measurements of mechanical properties

Tendons have been shown to vary in their properties depending on age [57,58], weight [58] and levels of athletic training [59,60]. Properties of interest include spatial measures (the diameter and cross-sectional area, tendon length and moment arm of the calcaneus from the ankle rotation point), as well as the stiffness, force normalised strain and Young's modulus.

Testing to obtain mechanical properties is non-trivial due to the difficulty to directly measure the forces, elongation and even the simple dimensions of tendons *in vivo*. These factors are complicated by the non-linear mechanical properties of tendon, the non-uniformity of the tendon cross-section area and composition (as the tendon joins the muscle). *Ex vivo* experimentation on both human and animal tendons is also hampered by the difficulty in maintaining hydration levels similar to *in vivo*, degradation of the tendon outside of the body, the effects of temperature and the difficulty in clamping the ends of a dissected tendon securely and with a suitable stress distribution.

There is a notional characteristic shape to the stress-strain relationship for Achilles tendons as shown in figure 2.12. Initially there is a 'toe' region where the tendon has a low stiffness due to straightening the crimp (figure 2.2) that is visible at several levels of the tendon hierarchy. After this there is a near-linear region of elongation where the tendon fibres slide over each other and elasticity is from the cross linking collagen between fibres and from compression and friction emphasised by the spiral twist of those fibres. This extension is initially completely recoverable. In the final region of extension fibres truly slide over each other and some cross linking fibres begin to break. In this region the extension is somewhat recoverable but has increasing characteristics of plasticity as

the extension continues toward breaking point. Beyond this region fibres part from each other either gradually as a tear or suddenly as a rupture.

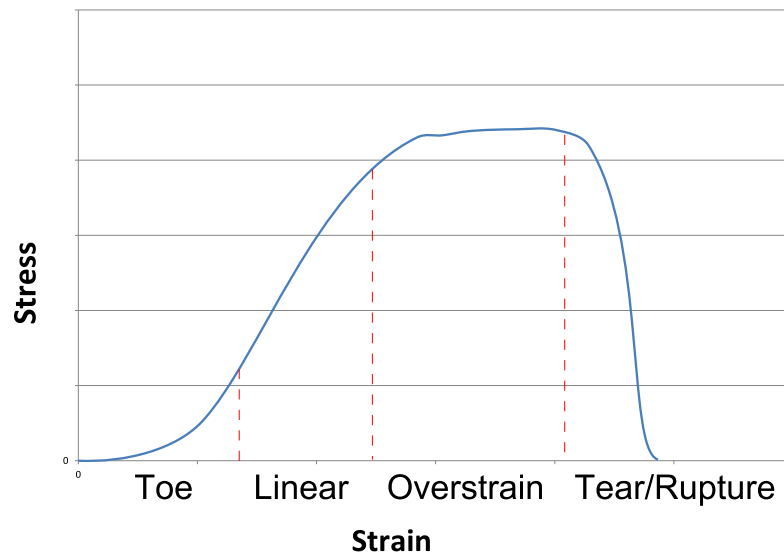


Figure 2.12: The notional non-linear stress-strain relationship for Achilles tendons under tension [4].

For the *ex vivo* studies, Abrahams' 1967 article [61] is widely cited. The paper defined speed dependent hysteresis in equine tendon, demonstrated the effect of the crimp structure with microscopy and conducted a controlled tensile test to destruction of a single cadaver Achilles tendon taken from a 54 year old woman within 24 hours of post-mortem, which was suspended in Ringer's solution (a saline solution intended to mimic *in vivo* conditions and maintain tissue hydration) and maintained at 37°C. Average cross-sectional area was calculated by taking the tendon volume (derived from fluid displacement) and dividing by the tendon length and was found to be approximately 60.6mm². The grip-to-grip speed of the tensile loading was aimed to be at 100% strain per min, but due to slippage or viscoelastic effects it was noted that the measured stiffness was lower than expected based upon experiments on horse tendons. They also noted that the original length of human Achilles tendons was recoverable as long as 2.5-4% strain was not exceeded.

These findings form the basis for much of the literature, but, as figure 2.13 shows, there is a great deal of difference in the literature regarding the shape, strain range and stiffness even from mean values of somewhat similar test subjects. For various described stress strain relationships investigated there is very little consensus on either the shape, the amount of hysteresis, the maximum values of strain that can be achieved or the stiffness

of the tissue. Widely different values of stiffness and elastic modulus are reported in the most recent *in vivo* and *ex vivo* papers from several groups. In figure 2.13, values have been used for the loading cycle of healthy adults and only included the mean values or ‘typical’ values shown in their figures. The results from Stenroth et al. [57], Waugh et al. [58] and Theis et al. [62], where there are different demographics or loading conditions have also been included. Where studies have only included force and extension data (marked by ‘*’) the mean cross-sectional area and mean tendon length of subjects had been used to convert to stress and strain. Figure 2.13 highlights the range of strains achieved, with greater than 10% strains being achieved in a number of studies. Figure 2.14 shows a close section of the 0%-5% strain range for these same studies and highlights that not only is there a great variation in the reported Young’s moduli (the stress-strain gradient), but that there is often a near linear response recorded rather than the non-linear response expected from *ex vivo* studies. This could indicate that *in vivo* studies are unlikely to include evidence of the non-linear toe region due to difficulty in finding a truly force-neutral foot angle, or that loading conditions can be such as to change that initial response.

Waugh et al. [58], Maganaris et al. [63,64], Stenroth et al. [57] and Lichtwark et al. [9] found largely linear responses with initial non-linear toe regions either being ignored or not apparent. Waugh, Maganaris and Stenroth all used very similar techniques of measuring ankle torque with a dynamometer during voluntary plantarflexion and tracking of features with ultrasound imaging. As an alternative Lichtwark et al. used a pressure plate to measure the force during one legged hopping. From figures in the paper by Stenroth et al. it can be inferred that fast elongation speeds of approximately 6% strain per second were achieved, whereas Maganaris had a speed of approximately 1.7%/s and exhibits a slightly more curved response.

There are several potential causes for the severe differences found by different groups. The differences could represent genuine differences in the groups of subjects analysed due to age or other factors. Although all groups recorded quite wide variance between subjects, the difference in mean values found by different research groups is extremely pronounced. Burgess [65], Kuo [66] and Stenroth [57] each had force extension curves for deliberately

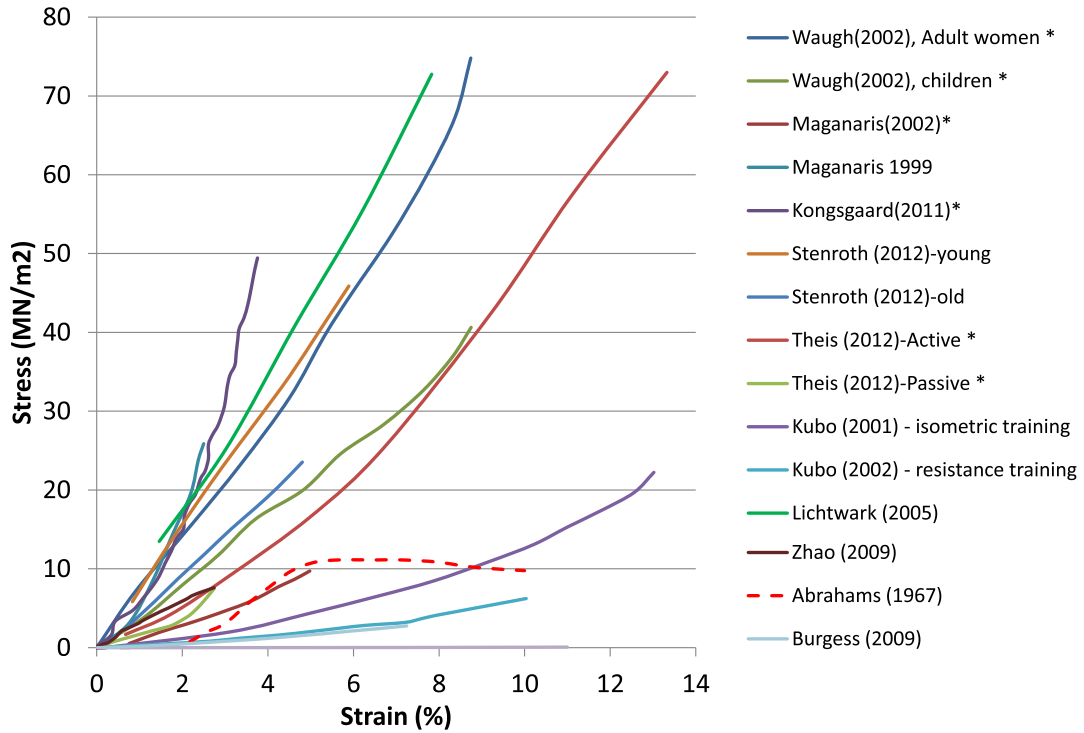


Figure 2.13: Mean Stress-Strain relationships found from *in vivo* (solid lines) and *ex vivo* (dashed lines) studies in 0-14% strain range. * denotes trends that have been based on force/extension data with mean CSA and lengths used.

different groups which had less variation (within their respective studies) then this seems unlikely. The suggestion, then, is that the methods provide different results. Generally, measures of cross-sectional area are reasonably consistent of being 55-70mm² for healthy adult Achilles tendon. This in itself is a wide range, accounting for approximately 25% difference in stress for the same force applied. Most *in vivo* studies involve the use of ultrasound to measure the CSA and this method is vulnerable to deformation of the tissue by the contact force and inter-user measurement variation from delineating the tendon from surrounding tissue. A few studies use the average CSA from three scans taken at defined points along the tendon. Again, this is open to methodological, operator and patient variation and may somewhat disguise a measure of maximal stress from the thinnest point, although it will more accurately represent a measure of energy storage throughout the whole tendon.

Theis et al. described in detail the importance of speed in the measurement of apparent stiffness [62]. They found that the stiffness (in the strain region that they defined) was affected linearly by speed of motion. The exact relationship would be expected to

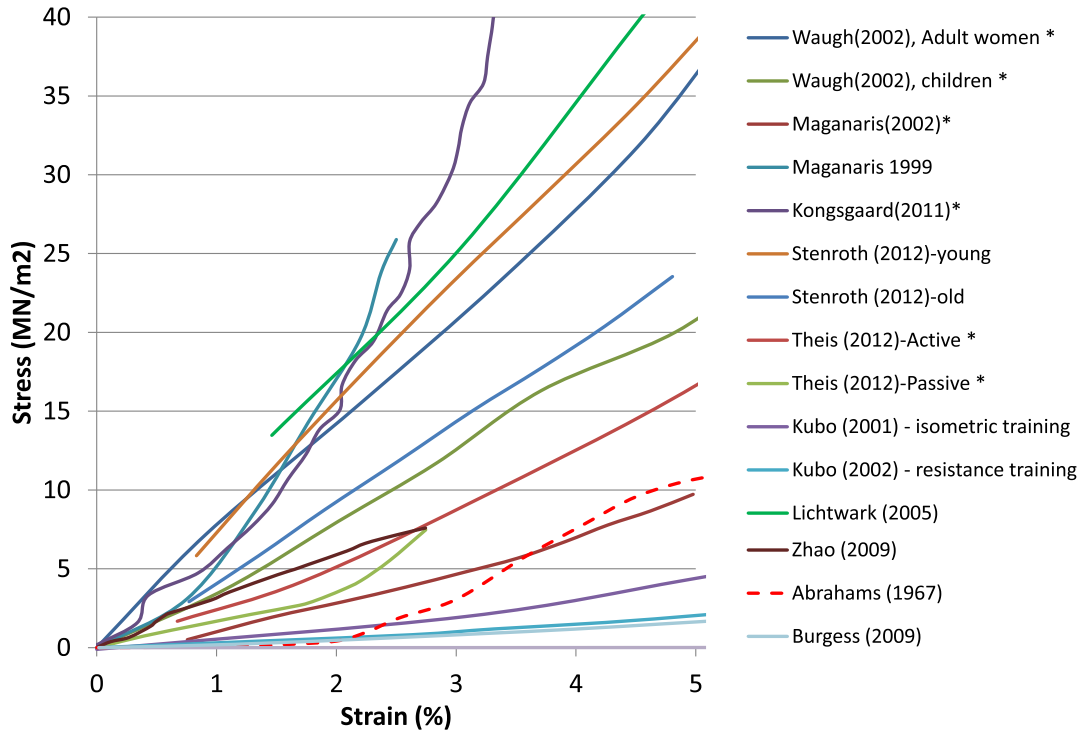


Figure 2.14: Mean Stress-Strain relationships found from *in vivo* (solid lines) and *ex vivo* (dashed lines) studies in 0-5% strain range. * denotes trends that have been based on force/extension data with mean CSA and lengths used.

change for different strain-regions and possibly for different subjects, but the finding is important as it suggests the possibility of comparison of results across different groups despite different acquisition speeds.

In summary, it is difficult to assess the true mechanical stiffness of the human Achilles tendon *in vivo*. Differences in methodology and reporting mean that reproducing numerical findings are not likely to be viable. The acquisition of and reporting of stress and strain information in a more repeatable manner would be of great benefit for accurate comparison of group studies and would lead to an improved understanding of the effects of loading, training, therapy, disease or age upon the Achilles tendon.

While numerical analyses are of great significance, there are also qualitative questions to be answered about motions and strains within tendons. For example, some groups have used simple point based tracking strategies in ultrasound images to assess shear motion in tendons over large ranges of motion [67,68].

2.7 Chapter conclusions

This chapter has served to inform the reader of the key information about the Achilles tendon and to motivate the need for a non-subjective property measure of tendon tissue as a part of monitoring conditions. The key findings are:

- Described the tendon tissue substance and surrounding anatomy.
- Described the healing process post-rupture.
- Showed that there are various treatments either in current use or being developed that would benefit from an improved numerical assessment of their relative merits.
- Introduced basic mechanical properties as a measure of tendon function as used in previous *in vivo* and *ex vivo* studies.
- Demonstrated that there is a poor consensus for mechanical stiffness or Young's modulus of the Achilles tendon and that this variation may be due to inconsistencies in methodology between research groups, although it may be possible to reconcile some of these differences between population groups.

Chapter 3

Background Ultrasound technology

This chapter reviews the current state of the art regarding imaging techniques and technologies used to assess health in Achilles tendons for research and clinical purposes. This includes a review of alternative imaging modalities; a summary of ultrasound physics and ultrasound diagnostic image creation; some potential ultrasound techniques to measure tendon health that aim to rival elastography; a derivation of elastography and a review of the recent literature relating to the use of elastography for measuring tendon properties.

3.1 Alternative imaging modalities

There are several potential medical imaging modalities for assessing Achilles tendons *in vivo*: direct observation, optical imaging, soft tissue X-ray (and CT), magnetic resonance imaging (MRI) and ultrasound (US) imaging.

3.1.1 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is perhaps the most capable modality for imaging of soft tissue [69]. By using different imaging protocols (for example, T1 weighted, T2 weighted) as well as contrast agents, MRI can effectively distinguish many different soft tissues and generate accurate 3D volumes. MRI is not widely used in clinical assessment for musculoskeletal conditions (in the UK) due to its high cost and low availability for musculoskeletal assessment. MRI scanners are room-sized devices with high power usage and limited availability, which make it unlikely that they could be made widely available for use regular diagnostics or physiotherapy assessments. Clinical MRI also has relatively low spatial resolution, in the order of 1mm voxel spacing (unless using very high strength magnetic field MRI), and this resolution is dependent upon the strength of magnetic field and application (it can be from 50 μm to 10 mm [70]).

It is, however, possible to perform magnetic resonance elastography (MRE). Here, a mechanical shear wave is initiated in the tissue either by mechanical actuator at the

skin, focused ultrasound or acoustic speakers [70]. The shear wave is synchronised to the MRI pulse and the phase offset of the MRI response is proportional to the speed of the shear wave. This has been shown to have good sensitivity to motion in with a displacement resolution of the order of hundreds of nanometres [71]. The shear modulus (μ) of the tissue is found as $\mu = \rho v_s^2$, where ρ is the density of the tissue (assumed to be 1000kg/m^3) and v_s is the measured velocity of the shear wave. The Young's modulus (E) is inferred by $E = 3\mu$. Spatial resolution of the resulting strain imaging is typically $1/3$ of the resolution of the MRI sequence [70]. Recent publication rates on the MRE for musculoskeletal applications are relatively low and seem to principally be focused on muscle function and not on stiff tissue like the Achilles tendon [72–74]

Finni et al. have used MRI to study the calf muscle velocity on subjects with Achilles tendon rupture performing maximum voluntary plantar flexion [75] to analyse the relative muscle contributions as a post-rupture longitudinal study. Spatial measurement from MRI combined with dynamometry has also been used to estimate mechanical properties and indicate asymmetry of mechanical properties between left and right legs [76].

There is some perceived commercial demand for MRI that is specifically for limb analysis, and GE produces their Optima MR 430s series of scanners which specifically scan limbs. These scanners have a reduced diameter which allows lower power and reduced size yet produce similar strength magnetic fields (approximately 1.5T [77]) as larger systems and thus have lower operation cost. Due to the combination of tissue differentiation, bone penetration and full 3D image field availability, it is likely that MRI will continue to be a useful tool for assessment of complex conditions and injuries around the ankle, where pathology may not be restricted to a single tissue type or location.

3.1.2 X-ray and Computer Tomography (CT) imaging

X-ray imaging is commonly used in cases of trauma to assess if bone structure has been damaged. Although it has good spatial resolution, it has poor contrast for soft tissues and also has the negative effect of dosing the subject with radiation. Soft tissue can be somewhat better seen with X-ray Computer Tomography (CT) and recent advancements in technology have led to very low dose x-ray images being possible. These are frequently

used for assessment of blood vessels and cardiac imaging where it is possible to introduce contrast agents that can greatly improve vessel appearance. This image modality is not sensitive to different tissue types without additional contrast agents being used and so concerns could be raised of the ability to distinguish tendons from fat or muscle. Again, temporal resolution of static images is relatively low and acquisition of many X-ray images on a single subject is not desirable due to the radioactive dosing factor. However, cardiac images of 3D and 4D displacements are possible via cine CT methods [78]. Here, multiple frames are acquired of the heart at sequenced points of the beat cycle. There are low amounts of image texture in CT imaging, making it difficult to apply optical flow analysis, so methods which track edge features and corresponding apply models can be applied effectively [79]. Such methods may be difficult to apply for musculoskeletal applications as tissue boundary features (curvature, links to other tissue) are not plentiful - which could lead to a sparse sampling to inform the model.

The principal factors of radiation dosage and equipment size limit the potential use of X-ray and CT images, although their relative cheapness, availability, familiarity and usefulness in identifying bone trauma means that they will continue to have a place in clinical practice to observe and assess conditions, but not for frequent monitoring.

3.1.3 Optical imaging

Optical imaging has advantages of high resolution 2D and even 3D images which can more intuitively be verified or interpreted due to the familiarity with visual media. Moreover, the advances in both research and commercial technology in recent years has made optical hardware of exceptional quality available for research applications. Near infra-red (NIR) has a relatively good penetration depth of up to 20mm, and recent work into the photo-acoustic effect has managed to combine some of the benefits of the penetration depth of ultrasound with the good resolution of optical imaging [80]. Initial reviews of the literature suggest that these techniques are largely being employed as research tools akin to other microscopy methods; for Achilles tendon research they are used in investigations into vascularisation or collagen alignment in tissue [81].

3.1.4 Ultrasound imaging

Ultrasound imaging has made great advances in the last 20 years, with a greater range of ultrasound probes being made commercially available by various manufacturers that allow different fields of view, faster frame rates and higher frequencies to be used. This means that 2D ultrasound probes with a wide, square (not conical) field-of-view and capable of $>10\text{MHz}$ frequency are available on most ultrasound platforms. For superficial (close to the skin) tissue, like the Achilles tendon, images are easily generated that clearly show the tendon and surrounding tissue with discernible textures. 3D probes are also available, although at the cost of lower frame rates and usually lower spatial resolution.

Ultrasound devices are also becoming much more available to the medical profession, being much cheaper than MRI or CT, are safe for multiple acquisitions from subjects and compact in size (typically the size of a laptop). Very small and low cost units are coming onto the market which may be pocket sized screens with probes attached. At the time of writing however, the image quality from such units appears low and the power gain and probe options are limited. GE are using new rapid prototyping techniques which promise the capabilities to further reduce cost and make bespoke probes more possible [82]. Further usability issues are being addressed by incorporating electronics technology into ultrasound systems such as wireless probes, increased data processing capabilities and increased data storage. Assessment of tendon health based upon B-mode ultrasound grey scale images alone has been shown to assist diagnosis by measuring [83, 84].

While all of these aspects are highly positive, it is by far the most ‘noisy’ of the imaging modalities described. The speckle seen on ultrasound images is not a true time-based random noise; it is a spatial interference pattern defined by the characteristic distribution of ultrasound scatterers upon the ultrasound signal as it travels through the tissue. In addition, appearance of tissues and tissue boundaries is highly direction dependent, reducing the sensitivity and selectivity with which different tissues can be identified. Deep tissues are additionally affected by signal attenuation and sound waves can only minimally penetrate bone (for instance, brain features are visible in a foetus with ultrasound imaging, but adult brains are usually not).

3.2 Ultrasound background theory

This section covers the fundamental principles of diagnostic ultrasound imaging. It is important to be aware of the important factors involved in creating ultrasound images as they are inherently anisotropic and are not captured in the same way as natural images from photography or other medical imaging modalities. A general reference for much of this information is from Halliwell's '*A tutorial on ultrasonic physics and imaging techniques*' [85].

3.2.1 Pressure waves and signal response

The ultrasound signal is a longitudinal pressure wave that causes a sinusoidal acoustic oscillation in the tissue it passes through typically in the frequency range 2-40MHz. Due to this signal frequency range and the compatibility with electronic circuits and signal analysis from the area of radio frequency analysis, this is usually referred to as the Radio Frequency (RF) signal. Deep tissue ultrasound images are possible as these sound waves can cohesively propagate within soft tissue and yet be affected by it so as to give a characteristic response. The energy of the sound wave does not penetrate entirely as tissues will absorb, reflect, and scatter these waves differently depending on their properties and so the return signal is a function of the materials that are encountered. These pressure waves can be described in one dimension by the (pressure) wave equation (equation 3.1) which denotes that the pressure wave will be dependent on position in the field of interest, the time of propagation and the speed of sound in the medium.

$$\frac{\partial^2 P(x, t)}{\partial t^2} = c^2 \frac{\partial^2 P(x, t)}{\partial x^2} \quad (3.1)$$

where P is the local pressure and c is the speed of sound in the tissue, which is related to the tissue properties by equation 3.2.

$$c = \sqrt{\frac{k}{\rho}} \quad (3.2)$$

where ρ is the tissue density (kg/m^3). k is the bulk modulus of the tissue (Pa), the material property that describes the resistance of a substance to compression in all three

axes ($k = \rho^{dP}/dV$ where V is the volume). The three key material properties are bulk modulus, elastic modulus and Poisson's ratio, any two of which can be used to define the third. For image reconstruction, the speed of sound is usually assumed to be relatively constant throughout the tissue and tissues are assumed to be isotropic. Real tissues are not truly isotropic and homogeneous, which could potentially lead to significant distortions in measurement from ultrasound images; different tissues have been shown to have varying speeds of sound [86] and in tendon for the speed of sound to alter significantly (from 1580m/s - 1860m/s) depending on the direction of the sound wave [66].

In a homogeneous fluid, the compression wave created will be sinusoidal, with period T and frequency f where $f = 1/T$ and wavelength $\lambda = c/f$.

Diagnostic ultrasound transducers act as both transmitters and receivers of ultrasound pressure waves. In a tissue, some of the ultrasound energy will be reflected back to the transducer as the pressure wave passes through. This return pulse is read by the transducer and translated back into an electrical signal. As a constant speed-of-sound is assumed, the time delay from the return pulse is equated to the distance seen in the image. For example, consider a single element transducer being suspended in a flask of water 5cm from the bottom. The ultrasound pulse will travel to the bottom of the flask, reflect off the surface and return to the transducer. The return journey time for a sound pulse will be $1540m/s / 2 \times 0.05m$ and the receiver will read the strong response of the return pulse signal at that time. If the flask is then filled with a solution with small suspended particles that scatter ultrasound waves (such as talcum powder) then some of the sound energy will be reflected and scattered at each point along the signal path. The return ultrasound signal will therefore be more complicated. If the scattering particles are not homogeneously spread or the particles have differing size distributions over distinct areas, then the signal response will be non-uniform with responses of different amplitudes and phase shifts. This is the essence of ultrasound imaging - that different tissues return different responses to ultrasound stimuli.

The return signal is a function of several factors - reflection, refraction, attenuation (absorption and dissipation), diffraction and scattering. *Reflection* is intuitive and describes the energy that fails to penetrate a tissue boundary and is returned toward the

transducer. Reflection can cause image artefacts due to reverberation, where doubly reflected signals will appear to add texture to deeper tissue - this is responsible for some apparent tissue texture seen in bone on ultrasound images. *Refraction* is rarely considered in image reconstruction but describes that the sound wave path may bend due to changes in tissue density. *Attenuation* describes energy that is not returned to the transducer as it is *absorbed* and *dissipated* by the tissue. Higher frequency ultrasound pulses attenuate faster than lower frequencies. Dissipation describes the fact that sound waves progress in a spherical or cylindrical form from the source and so amplitudes are proportional to distance from the source (R) by a $1/R^2$ or $1/R^3$ relationship. *Diffraction* and *scattering* are linked, describing the mechanisms that cause a sound pulse to dissipate due to interaction with 'scatterers' in the tissue and cause an interference pattern. Scattering is assumed to follow a Rayleigh model (the same as used to describe light scattering in the atmosphere) and so statistics of the amplitudes of the return signals should follow a Rayleigh or Nakagami distribution [87]. This distribution is practical for the majority of tissues, but there are exceptions particularly for non-homogeneous or anisotropic tissues or where there are mixtures of tissues [87]. These issues are important to note, as any spatial measurements from ultrasound images will have an inherent characteristics because of them, and that some of those characteristics may be difficult to predict, leading to system error.

3.2.2 Tissue boundaries

Ultrasound images often have a bright response at the boundary between tissues. This is due to a large change in acoustic impedance.

If tissue properties, such as density and bulk modulus change suddenly, the sound does not transmit well and a great part of the energy is reflected. The greater the acoustic impedance difference, the greater the amount of reflection. This is particularly noticeable for soft tissue/bone boundaries and for air/skin boundaries. The acoustic impedance at the skin boundary is matched using ultrasound gel (although de-gassed water works well), without which insufficient acoustic energy can be sent or received to obtain an image [85]. This type of reflection is known as *specular reflection* and reflects the acoustic energy at an angle of reflection equal to the angle of incidence.

3.2.3 Scattering

Scattering is the effect that provides distinctive texture to tissues. The fine texture pattern seen in images is usually not a true resolution of sub-structure, but an interference pattern of complex interactions of the ultrasound signal. The model used to describe this is Rayleigh scattering, where there are spherical particles with diameter much smaller than the wavelength of the ultrasound pulse, typically $<10\%$ of the wavelength. Ultrasound wavelengths are typically of the order of $100\text{-}300\text{ }\mu\text{m}$. The intensity of the return signal in a field of identically sized scatterers can be described as a function of distance, wavelength, acoustic properties of the tissue, particle size and density of scatterers in the tissue, and polarization properties of the scatterers (equation 3.3) [88, 89].

$$\frac{I}{I_0} = \left(\frac{1}{2R^2}\right) \left(\frac{2\pi}{\lambda}\right)^4 \left(\frac{n^2 - 1}{n^2 + 2}\right)^2 \left(\frac{d}{2}\right)^6 N_p (1 + \cos^2\theta) \quad (3.3)$$

where I is the intensity, I_0 is the intensity at the source, R is the distance between the particle and the observer, n is the refractive index, d is the scatterer diameter, λ is the wavelength of the ultrasound signal, and θ is the angle between the transmitter, the scatterer and the receiver (notionally π radians for diagnostic ultrasound). This description shows the importance of wavelength and scatterer diameter upon the return signal strength.

If much lower wavelength (higher frequency f , as $f = c/\lambda$) ultrasound is used, then the intensity spectrum of the return signal will also be influenced by Mie scattering which has different properties [90]. There are fluid properties that affect the response as well: Rayleigh scatterers with similar density but different compressibility to surrounding fluid will dissipate incoming ultrasound energy as a radial monopole rather than specular reflection or continued onward transmission through the media. If the scatterer has different density but similar compressibility to surrounding fluid, the energy will be dissipated as a dipole source.

In reality, the nature of tissue makes the returned scattered signal complicated. Cells and other small sub structures in a real tissue have a range of shapes, sizes, densities and refractive indices. The dissipation of energy from multiple and densely packed scatterer

sources means that secondary interactions do occur, and histograms of tissue responses usually have noticeable noise. It should also be noted that there is a texture to tissue seen with ultrasound imaging, and that this texture is characteristic of the tissue but it is *not* necessarily an accurate descriptor of explicit structure.

3.2.4 Wave propagation and signal phase

Ultrasound waves are created as being sinusoidal, however, the phenomenon of *dispersion* distorts the shape of the compression wave. As previously shown, the speed of sound is related to the density of the tissue, but the pressure wave distorts the density minutely. This means that the particle at the wave peak velocity moves faster than the rest of the signal, making the signal shape become more saw-toothed as the wave progresses [85] (figure 3.1). This is seen as a shift in phase from the tissue in deeper tissue. This effect is small, but there are additional shifts in phase due to small changes in speed of sound in different tissue types.

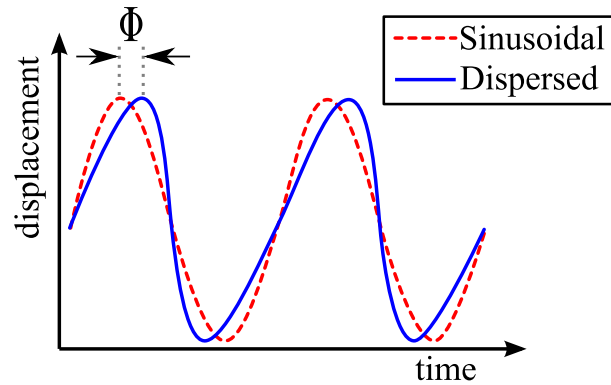


Figure 3.1: Illustration of how dispersion occurs in a sinusoidal wave. The compression part of the wave travels faster than the rarefaction so the wave becomes more more saw toothed. Φ is the apparent phase lag.

3.2.5 Transducers

A single element ultrasound transducer has a single piezoelectric crystal. Piezoelectric materials exhibit a direct link between their mechanical and electrical state, which results in mechanical stress causing a temporary charge difference across it which can be read as a voltage. The reverse is also true, and an alternating electrical current (AC) will cause the face of the transducer element to oscillate. The frequency of the oscillation is dependent on the frequency of the AC current, but greater responses are possible if the resonance of

the material (defined by its material type and spatial dimensions) is well matched. For this reason each US transducer will usually only transmit or receive ultrasound waves at set frequencies.

In an imaging transducer, an array of piezoelectric elements is required. To ensure as similar properties as possible, a single large crystal is grown under controlled conditions and then sub divided into elements with a very fine saw or by chemical etching. Spacing between transducer elements are typically of the order of $10\mu\text{m}$. A backing material is placed in contact behind the piezoelectric elements to provide damping of resonances and an acoustic lens is placed in front to focus the ultrasound energy and protect the elements. These are passive materials and are only controlled by material selection and dimensions but aid signal clarity.

When the reflected ultrasound energy returns to the transducer, the transducer elements are mechanically stimulated and a signal voltage is created. These return signals are frequency bandpass filtered, tuned to a particular frequency with some broadband response. Many commercial systems are capable of ‘listening’ at two or more frequencies (either independently or simultaneously) according to the natural frequency of the piezoelectric elements and the resonant frequency of the receiver circuit. ‘Harmonic imaging’ is a method that combines the signal responses from two or more response frequencies, which has the benefits of the high resolution image in the superficial field, and the greater penetrating capability of lower frequency return pulse.

3.2.6 Beam steering and focusing

Simultaneously fired transducer elements form a pressure wave front that approximates the shape dictated by the transducer’s geometry (see figure 3.2(a) for a linear transducer). By firing the transducer elements in a timed sequence, the transmitted beam can effectively be steered to form a different angle (figure 3.2(b)). This technique is largely used for imaging deeper tissue where obtaining line-of-sight may be more difficult while maintaining acoustic contact, and is thus rarely used for imaging Achilles tendons. Sequential firing of the transducer elements can also be used to change the shape of the wave front, which can help adjust the effective focus to increase field-of-view or decrease dispersion

(figure 3.2(c)).

In the near field the maximum amplitude will oscillate, but it is assumed that the image is effectively in the far field region where amplitude will decay gradually and not oscillate.

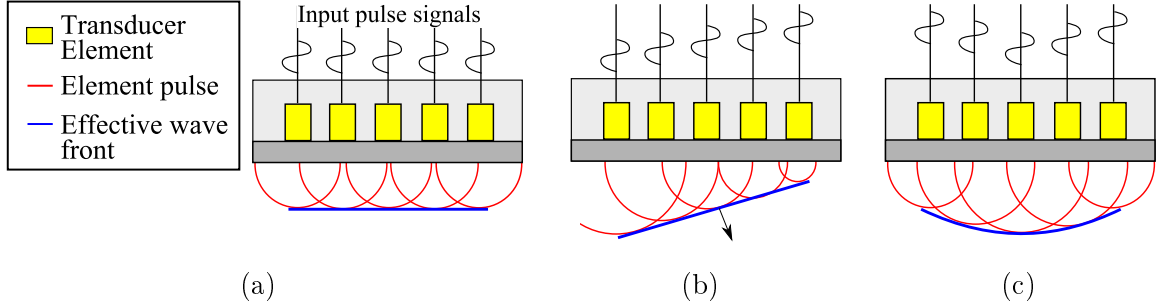


Figure 3.2: (a) Illustration of straight wave front. (b) Illustration of angled wave front generated by beam steering. (c) Illustration of curved wave front generated by beam focusing.

3.2.7 Field-of-view

For a linear probe (used in this thesis) the ultrasound image will occupy a square field-of-view. For deeper tissue (i.e. organ or fetal imaging), a conical field-of-view is more common. A 2D image is not truly an infinitesimal slice. The return signal is a function of the volume that the ultrasound wave passes through and this volume has a variable thickness (referred to as the ‘elevation’) and a minimal width which is the elevation focus. Although the elevation does vary, a constant slice thickness is usually assumed. The direction along the length probe (image width) is referred to as *lateral*, and in the direction of the signal (image height) as *axial* (figure 3.3).

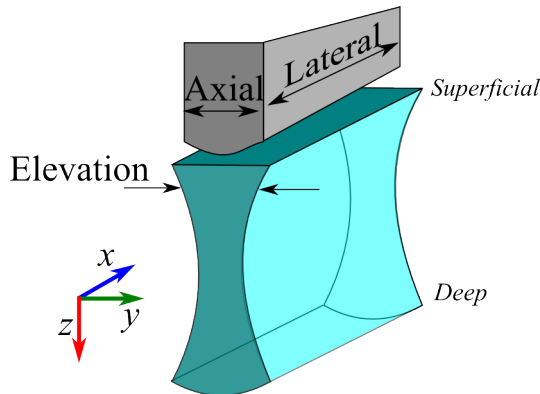


Figure 3.3: Illustration of ultrasound probe, field-of-view and axes terminology.

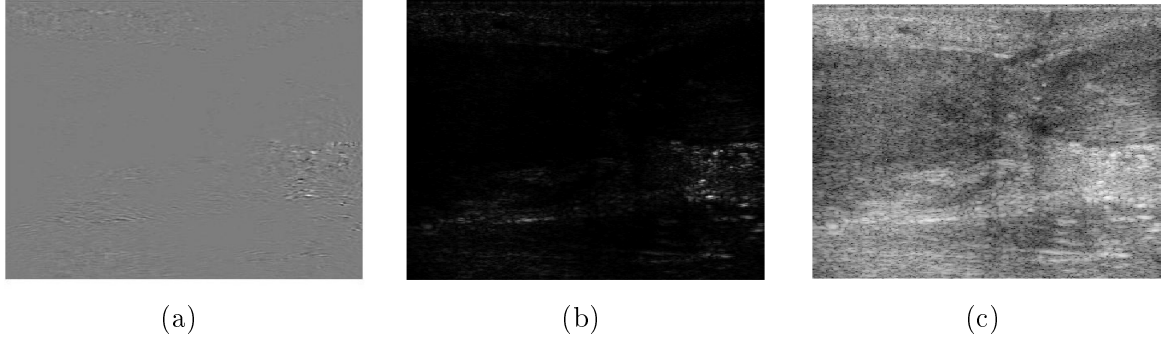


Figure 3.4: (a) Example of 2D grey scale ultrasound image of RF domain. (b) Example of 2D grey scale of RF signal envelope obtained by Hilbert transform. (c) Example of log-compressed RF signal envelope.

3.2.8 B-mode images

‘Brightness modulation’ (B-mode) images are the 2D grey scale images that can be viewed to represent the tissue being viewed. To obtain them, the return ultrasound signal needs to be processed. Once the return ultrasound signal information has been received, it is digitally sampled and stored as a 2D matrix of values. This is the radio frequency (RF) domain image and viewing it directly offers little insight (figure 3.4(a)). This signal can be represented a sinusoids of the form described by:

$$f(t) = A \cos(2\pi ft + \phi) \quad (3.4)$$

where f is the signal frequency, A is the amplitude, t is time and ϕ is the phase delay.

Alternatively, this can be conveniently represented as a phase vector of real (Quadrature-Q) and imaginary (or in phase - I) parts with a phase angle Φ , where the phase angle and amplitude change with time as a function of the underlying tissue (equation 3.5).

$$F(\Phi) = Ae^{i\Phi} \quad (3.5)$$

For a complex system, these phasor values are found using a discrete Hilbert transform. This ‘IQ’ representation allows for the fast extraction of the exact amplitude (the *signal envelope*) and phase information from the original signal at every point (figure 3.5).

From this representation the signal amplitude is taken and the phase information is ignored - note that this is disregarding any information that is a function of the signal

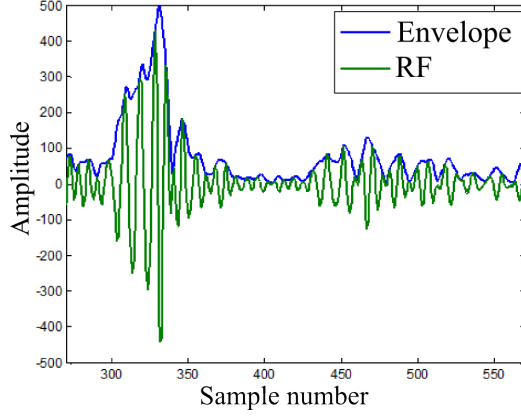


Figure 3.5: 1D example of RF signal and signal envelope found by Hilbert transform.

and that therefore potential tissue distinguishing information is lost in B-mode images.

The amplitude information alone still does not provide a satisfactory image, as peak values from echogenic materials and tissue boundaries vastly dominate. The amplitude of the signals is therefore log-compressed (equation 3.6). Finally, the images are normalised and quantised to the 256 levels of an 8-bit image.

$$B_{mode} = 20 \times \log(\text{abs}(\text{Hilbert}(RF))) \quad (3.6)$$

Other operations are often applied to improve the perceived image quality. These include (but are not limited to) compensation for attenuation (*time gain compensation* [91]), 2D Gaussian or median filtering of the resultant image, contrast enhancement (remapping values) and temporal filtering for speckle reduction. These aim to make the image more aesthetically pleasing, but may also reduce the distinctiveness of the signal relating to a specific tissue.

3.3 Image planes

Ultrasound images can be generated in any arbitrary plane, but conventions exist that they should either be in a recognisable axis of the body or of the tissue/organ being assessed. These planes are: sagittal, coronal and transverse planes (figure 3.6). For Achilles tendons, sagittal and transverse planes are the most clinically relevant. Note that in medical terminology the term ‘lateral’ is also used to denote a direction further from the centre of the body - this definition is avoided in this thesis for clarity and ‘lateral’

is only used to refer to the ultrasound image direction.

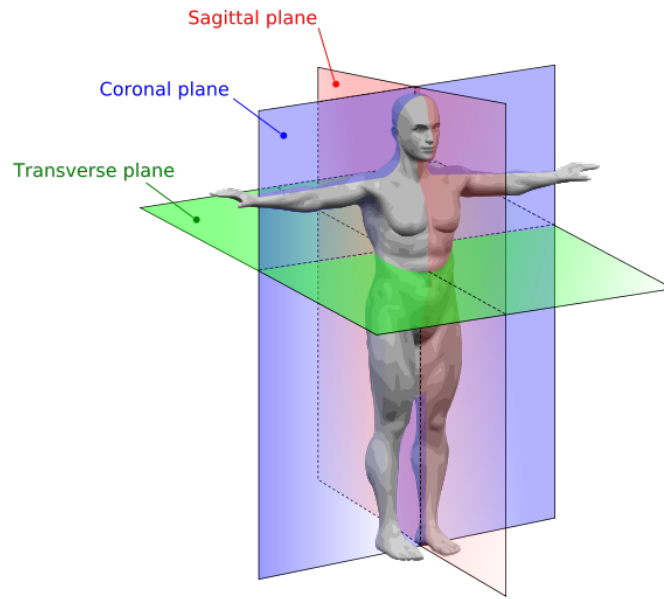


Figure 3.6: *Planes of view relative to human anatomy.*

3.4 The appearance of healthy and ruptured Achilles tendons in ultrasound images

Healthy Achilles tendons are anisotropic structures which have a bright, laminar textured appearance when the tendon direction is approximately in line with the lateral direction of the image (figure 3.7(a)). The boundary to the surrounding tissue is occasionally visible as an additional bright layer, but often it is only the texture and a small change in mean grey scale value that distinguishes the tissues. If the tendon is ruptured this isotropic appearance is significantly disrupted: the tendon appearance is darker, with disoriented fibres and often a dark blood clot (haematoma) which can cause shadows beneath it (figures 3.7(b)-(d)). The bulbous end of the tibia is usually visible in the same area as the tendon rupture which can aid orientation, but the calcaneus (figure 3.7(e)) is usually not in view unless a very wide ultrasound probe is used. As the tendon heals, the texture of the tendon becomes more uniform and darker as old tissue is necrotised and new tissue is reconstructed [92,93]. For further example B-mode images along the healing process see appendix A.

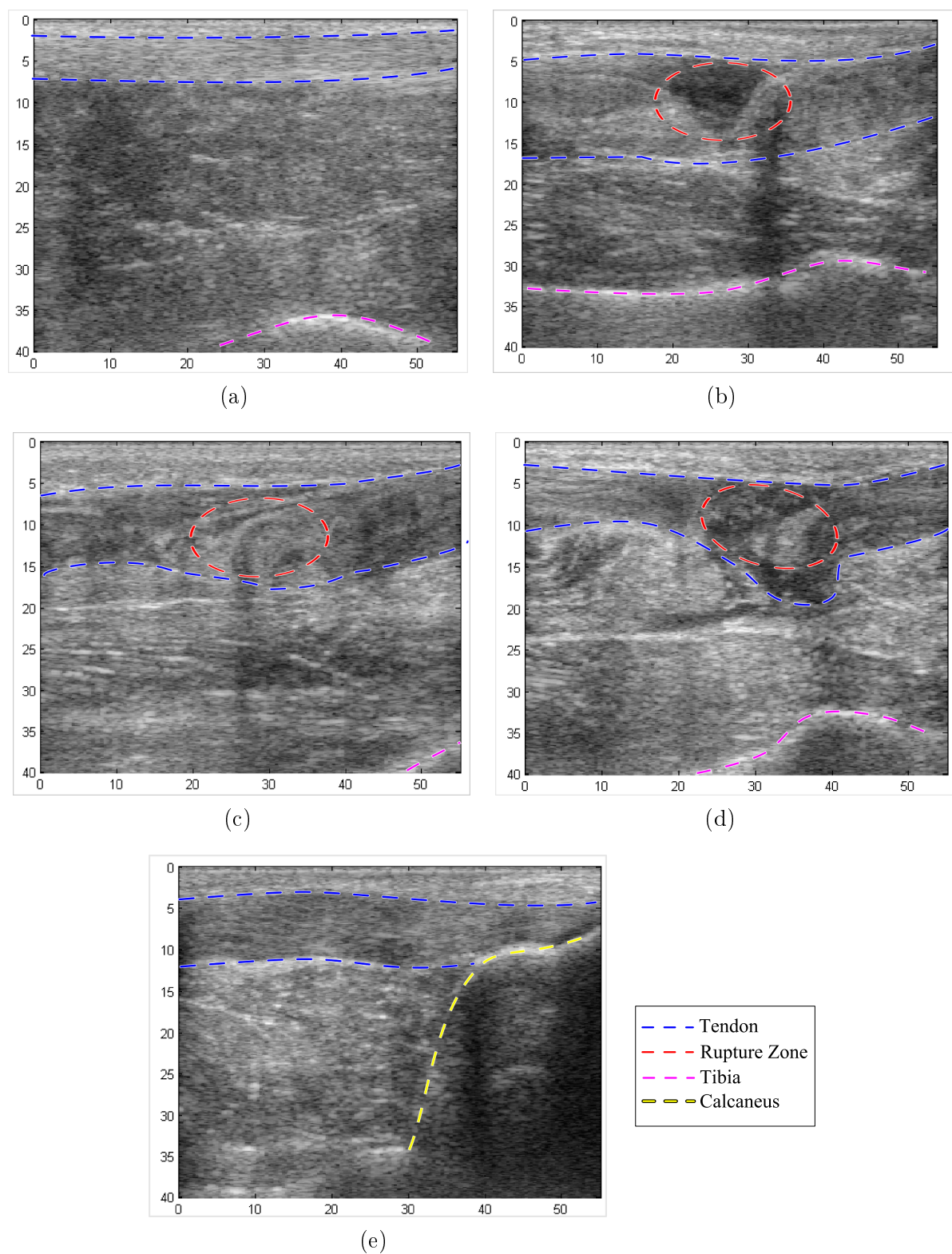


Figure 3.7: *Example B-mode images of Achilles tendons with significant areas labelled. (a)Healthy. (b)-(d)Recently ruptured. (e)Recently ruptured tendon with insertion to the calcaneus in the field-of-view (rupture zone not in field-of-view).*

3.5 Tendon measures of functionality from ultrasound

There is substantial interest in measurement of tendon health and particularly in using the properties of ultrasound waves or ultrasound imaging to establish changes in material properties of the tendon. Briefly, some of the competing research is described in the following section.

3.5.1 Tendon grey scale dynamics

Assessment of the B-mode images is a standard method for initial assessment of damage to Achilles tendons, being shown to be of benefit for assessing partial ruptures [94], tendinopathy, and as a decision making tool to guide surgical intervention [32].

When tendons are stretched, the fibre density changes and thus the appearance also changes. Duenwald et al. [95] have demonstrated that the strain experienced in porcine digital flexor tendons showed positive correlation with the change in B-mode intensity. However, subsequent studies have shown that this effect changes with damaged tendons [96] and that correlations across groups of human subjects *in vivo* have poor correlation [97]. It is therefore likely that any method of approximating strain estimation by grey scale value will require a calibration to the individual which may not be feasible.

3.5.2 Tendon anisotropy measures

Healthy tendon appears bright in B-mode images when the tendon fibre direction is at right angles to the signal direction. The reflection intensity is direction dependent as noted by Connolly et al [98], who used beam forming to ensure the maximum reflectivity occurs in deep biceps tendons and improves image quality for distinguishing tissues.

Garcia et al. [99] exploited this in their study on a damaged equine tendon. They used a single transducer system (non-imaging) to emit a broadband ultrasound pulse at healthy and damaged areas of a horse cadaver tendon in a water bath. The tendon was presented to the probe at many angles at ten degree increments and the normalised power spectrum density of the reflected signal calculated for each angle. The healthy tendon, being highly anisotropic to reflection, showed a large dependence on angle to reflection

power, whereas the damaged tendon section showed more consistent signal power return at different angles [99]. This result was replicated by Riggin et al [100] using a high frequency (55MHz) single element transducer on damaged mouse tendons.

This approach has some advantages over a full imaging system in that the hardware is very cheap, computational cost is low and high frequency transducers are more available. It could also be possible to build in a reflection intensity change over a range of angles using beam forming in an imaging system. Making such an analysis, a quantifiable measurement would require a substantial amount of validation.

3.5.3 Tendon texture image analysis

Image texture analysis is also being researched as a potential metric for tendon health. Van Schie et al. took stacks of transverse plane images of 26 subjects with tendinopathy and of 26 healthy subjects and compared 4 different custom texture descriptors “based on the stability of intensity and distribution in contiguous transverse images”. [101]. They found good differentiation between the groups for their metrics. However, they have yet to demonstrate sensitivity to changes over time or predictive capability.

3.5.4 Speed of sound

Different tissues have been shown to have different speeds of sound [102] and anisotropic tissues like tendon have been shown to have different speeds of sound depending on the relative angle of the ultrasound wave direction (i.e. sound moves faster along the fibre direction than across it) [66]. It is probable that this property and the anisotropy However, as the exact composition of each tissue is unknown it is impossible to represent this precisely and a global speed of sound is assumed (usually of 1540m/s).

Methods have been proposed to calculate the local speed-of-sound for specific tissues, either by adjusting the assumed global value and assessing the sharpness of the resultant image [103], image deconvolution [104] or refraction measurement by registration of images acquired at different angles using beam forming [105]. Using alternative hardware Pratt et al. have developed ultrasound tomography which can produce parametric images of speeds of sounds [106].

Although interesting, speed of sound assessment techniques have not yet shown themselves to provide useful parameters for assessing tendon damage, and further work would be required to establish this.

3.5.5 Force measurement

Measurement of overall forces in the Achilles tendon *in vivo* is not trivial and has been attempted by a variety of methods. Direct implantation of a relatively large strain transducer into the tendon has been reported for animal studies [107]. While this could provide accurate strain measurements, the mechanics of the tendon may be altered by the implantation (and resultant trauma response) and planar alignment of the transducer becomes significant. For human studies there are also important ethical issues and this invasive method is unlikely to be useful in a clinical or veterinary application.

Attempts have been made to use an optical fibre transducer as a minimally invasive method to measure forces [108]. In this method, a small (0.5mm diameter) optical fibre was implanted subcutaneously, and the return signal of transmitted light is recorded. Komi et al. [108] noted a linear relation of light intensity receiver voltage with static force as applied to an *ex vivo* rabbit limb due to buckling of the optical fibre. The smaller size of this transducer made it more acceptable to patients as it removes the need to allow the implantation site to heal for several weeks. It also allows the study of forces at sites other than the Achilles. However, the validity of this method in humans has been revised, with non-linear relationships of output to force, hysteresis, cable migration, tendon creep and skin loading artefacts all being observed [109]. Of particular note is that for Achilles tendons, migration of the optical fibre can cause RMS errors up to 27%, and fast loading rates (circa. 1000N/s) up to 17% error [110].

The most popular method is to measure forces where they are applied to (or by) the foot is by a dynamometer or foot plate [9,62,63,111] and a simple mechanical model is applied to infer the forces in the tendon. This has the key advantage of being non-invasive but may be inaccurate as the load distribution between the foot, ankle and leg tendons, muscles, skin and bone is complicated and loads may be differently distributed between different patients, particularly when suffering from trauma or disorders.

There is therefore a desire to infer forces, stresses and strains from less direct methods, although some of these are still invasive. An example of this is the radiostereometric analysis (RSA) where small tantalum beads are sewn directly into the tendon [31,111,112]. Strains are then measured in three dimensions by taking a dual-plane radiographic image in loaded and unloaded states. This is less invasive than direct implantation of transducers but still requires surgery and X-ray dosage, yet is also limited in that it cannot perform dynamic analysis (which may be of interest if viscoelastic properties are of interest).

3.6 Ultrasound elastography

Ultrasound elastography is a method of estimating local strains in tissues from a sequence of ultrasound acquisitions and is the proposed primary method for investigating the effect of healing in ruptured Achilles tendons in this thesis. The aim is to measure the strain within the tendon (as in the RSA method) but also to make use of the distinctive appearance of tissue in ultrasound imaging to remove the need to implant any foreign material. Strain measurement from ultrasound imaging is used in both medical applications to assess tissues and to analyse engineering materials [113].

Elastography algorithms comprise a local registration method (section: 3.6.1) which matches local patches of the image or signal from one frame to one or more successive frames and measures the displacement shift. When a force is applied to a tissue, the stiff tissue deforms less than less-stiff tissue. This rate of displacement can be used to estimate the local strain value (section 3.6.5) and can be super-imposed as a colour-map over the original B-mode ultrasound image. Quantitative values can then be obtained over a region of interest (ROI). Usually, elastography is applied by palpation from the ultrasound probe against the subject's skin, and while this is investigated (section 3.7), it has previously been noted in this thesis that the properties of the anisotropic tendon of greatest interest are along its length and this requires lateral elastography, presenting a different set of challenges (section 3.9).

3.6.1 One dimensional axial elastography

Consider a single column of linearly elastic, homogeneous material. The return signal value ($s_1(t)$) from any given point, i , can be expressed as:

$$s_{i,1}(t) = f(t - \tau_{i,1}) \quad (3.7)$$

where f is a characteristic equation of the column of material and τ_1 is the return signal time delay of the ultrasound pulse to the point in question [114]. If the column of material is displaced by an arbitrary amount, the return signal in the new time frame is:

$$s_{i,2}(t) = f(t - \tau_{i,2}) \quad (3.8)$$

Now assume that the time delay τ is only a function of distance (as a constant frequency value ultrasound pulse wave is used for each frame). Consider further that the two functions will locally be identical, $s_1 = s_2$, and the speed of sound is constant, then the displacement, d_x , is given by:

$$d_i = c(\tau_{i,2} - \tau_{i,1})/2 = c(\delta\tau_i)/2 \quad (3.9)$$

This is illustrated in figure 3.8(a).

When the compressions are small (assumed quasi-static), the local section of the signal will remain minimally affected and will look similar from one frame to the next. If perfect, exact point values could be read from the signal s_2 and the new time delay obtained. In reality the signals may distort slightly and signal amplitudes and phase will change. To overcome this, a short section or ‘block’ of signal samples from the post-compression frame signal (the ‘post-signal’) is taken and compared against the prior-signal (figure 3.8(b)). As the digital sampling only assesses the signal at discrete points, signal upsampling is often used to increase the accuracy, although at the expense of additional computational cost. Polynomial splines (usually cubic or quartic) are often used to interpolate values for upsampling as they offer a good compromise on accuracy for locally approximating a sinusoidal signal and are computationally inexpensive [115]. For additional increased

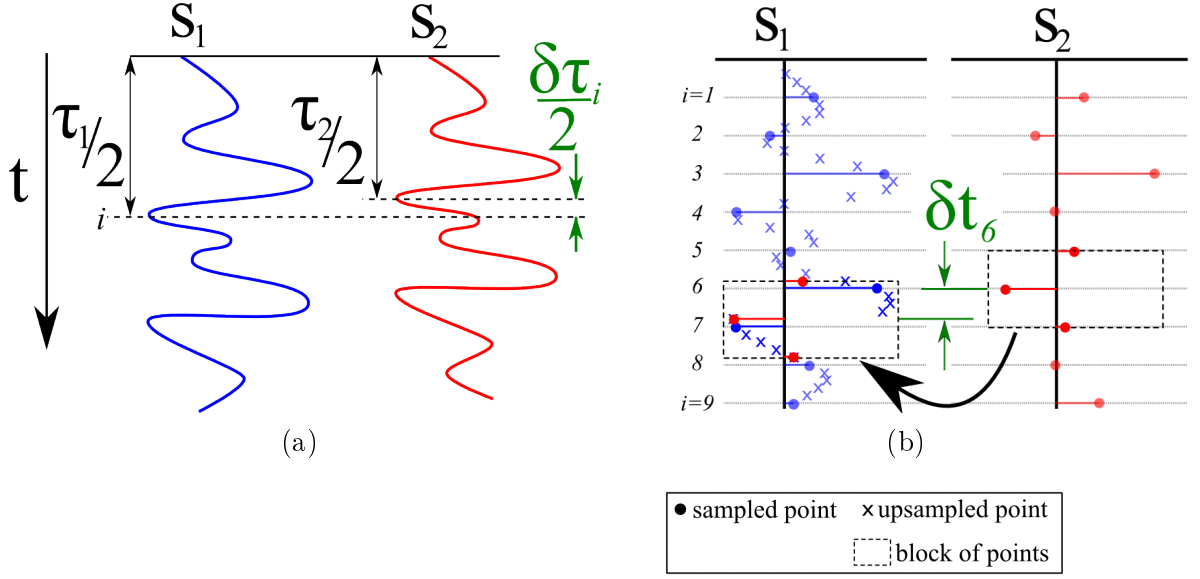


Figure 3.8: (a) Illustration of prior-signal (s_1) and post-signal (s_2) generated from two successive time-frames of ultrasound pulse-echo signals passing through a column of tissue. The tissue is compressed between signals, resulting in a measurable time delay change ($\delta\tau$) from the characteristic peak from the tissue at position i . (b) Digitally sampled version of signals; s_1 has been upsampled by a factor of 5 and a block of 3 samples of s_2 has been compared against it to find the delay associated with the point $i = 6$.

robustness, several parallel signal lines may be considered simultaneously in the 1D analysis.

3.6.2 Two-dimensional block matching analysis

This 1D method can be extended to two (or three [115–118]) dimensions. The origins of this methodology stem from optical flow methods from computer vision literature, and block matching was noted for its robustness in different imaging media and for being computationally efficient and robust in noisy image environments [119]. Here, local image-blocks (a small sub-section of image) are matched against regions of another image, usually one a small time step further on in a sequence. This can be used as a better characteristic for finding a global rigid transformation or for finding a dense or sparse non-rigid deformation field (similar to polyaffine registration [120]) for use in local strain analysis.

This requires three main components:

- A *cost function* as a measure of similarity or error between the block and the search region and additionally a regularisation cost associated with the expected type of

motion.

- A *transform function* which describes how the motion of the block is allowed to move and distort. This could allow for rigid translation and rotation for different scaling or skew of the sample. Generally, block matching is performed as a highly localised registration technique and will usually only concern rigid body translation where small movements are anticipated.
- An *optimiser* which acts as a search function to find the minimum cost and associated transformation when comparing the image blocks to subsequent frames. This could be in the form of a comprehensive search or a gradient descent method.

This process is summarised in figure 3.9 [121].

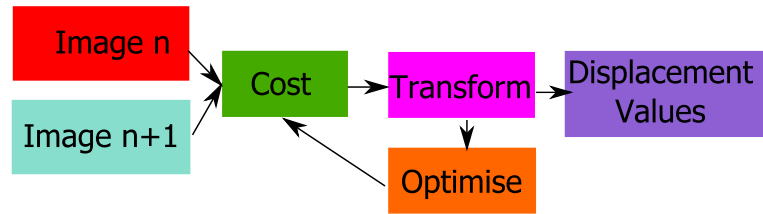


Figure 3.9: Flow diagram of general registration process.

For example, figure 3.10 shows two similar images, but with some of the image displaced. Here, block *A* has moved by a vector of $(2,0)$ and block *B* has moved by $(2,1)$. In this example the components of the image have only moved by rigid translation motion. The nature of ultrasound imaging adds some debate upon the strategies involved to track

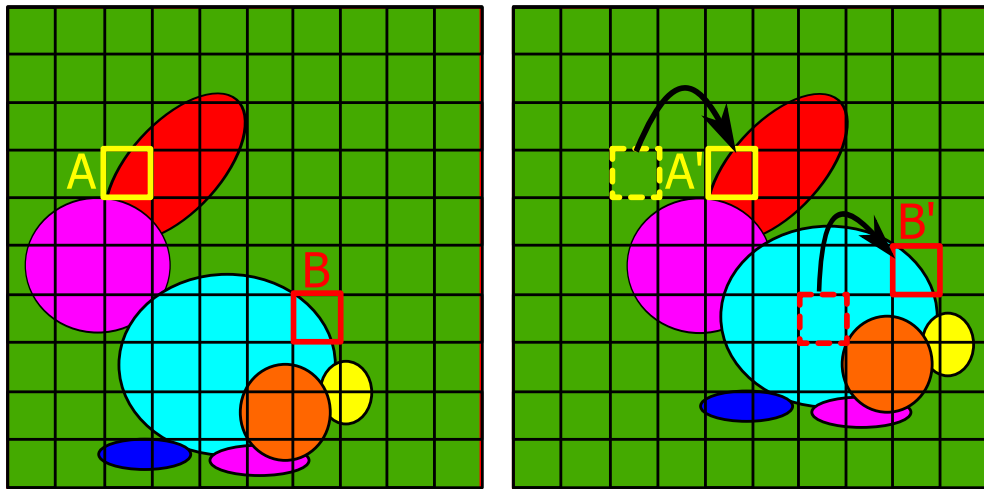


Figure 3.10: Illustration of 2D block matching to assess 2D motion.

displacement of signals. For instance, it needs to be decided whether to analyse the RF signal in the axial direction and the signal envelope in the lateral direction [122], or the RF signal in both directions, or to generate synthetic lateral phase (SLP) to allow phase comparison to be possible in two dimensions [123, 124]. Additional consideration needs to be made for the fact that pixel dimensions will not be equal and that resolution is much higher in the axial direction than the lateral (dependent on transducer frequency and element spacing).

It is tempting to treat two-dimensional elastography like digital image correlation (DIC) techniques used to assess surface strains in natural images [125], but it should always be maintained that the underlying physics is significantly different between the image directions, which does impact on the appearance of strain images.

Block matching is not the only method for finding image-to-image displacements. Other registration techniques are possible [126]. These methods include the diffeomorphic demons algorithm [127], which can include using temporal regularisation [128], Markov random fields frameworks [129], groupwise registration [130] and use of log-Euclidean polyaffine frameworks [120]. An exhaustive comparison of these techniques has not been conducted in support of this thesis.

3.6.3 Cost functions

Considering two consecutive frames, it is unlikely that the signal samples from a tissue section will have exactly the same values in successive frames due to small variations. In order to compare the signal samples from the two time frames, a *cost function* quantify the difference between image sections is required. Note that the cost can be applied to any representation of the signal (RF, I/Q, signal envelope, B-mode or signal phase) but that this may affect the result.

Cost functions may also have a degree of regularisation built into them. This could be restrictions to prevent folding or other undesired behaviour or could simply be the incorporation of smooth interpolation for sub-pixel quantification.

Multiscale approaches are popular [131–133] as they enable displacement tracking functions to find a good fit for large motions at the low scale and retain the precision of

fine resolution image matching.

If a comprehensive search of the cost domain is being used, the sub-sample accuracy can further be increased by interpolating the cost domain [134]. Cost functions are usually mathematically simple functions set up to minimise computational expense. Common terms used are the sum of absolute difference (SAD - equation 3.10), sum of squared distance (SSD - equation 3.11) or normalised cross correlation (NCC). NCC is usually found for image processing by equation 3.12 [135,136] but can be more accurately found as the convolution of the prior and post signals (this is effectively performed by multiplication of the Fourier transforms of the signals). The NCC will provide a value of 0 to 1, where 1 is the greatest correlation and thus should be maximised, whereas SSD and SAD should be minimised.

$$SAD = \sum_{i,j} s_1(i, j) - s_2(i, j) \quad (3.10)$$

$$SSD = \sum_{i,j} (s_1(i, j) - s_2(i, j))^2 \quad (3.11)$$

$$NCC = \sum_{i,j} \frac{s_1(i, j)s_2(i, j)}{\sum_{i,j} \sqrt{s_1(i, j)^2 s_2(i, j)^2}} \quad (3.12)$$

More sophisticated cost similarity measures that are based upon measures of the image/signal texture content rather than the explicit values at discrete points have been used as local descriptors for registration methods. These include using Markov random fields [137], Hellinger distance [138], Rayleigh [139,140] or Nakagami [141] distributions. These have been shown to be beneficial in certain applications in that they may reduce the effect of signal noise upon block matching if the characteristic statistical response is more robust than comparing the raw signal samples directly. However, there is additional computational cost.

3.6.4 Search strategies and optimisers

There are two basic approaches to search strategies: a comprehensive search of a defined search region, or use an iterative solver as an optimiser. In a comprehensive search, the

signal block is compared along the length (or area for 2D analysis) to build up a local cost map (figure 3.11). The minimum/maximum cost value is then identified directly or can be additionally interpolated to increase resolution [117].

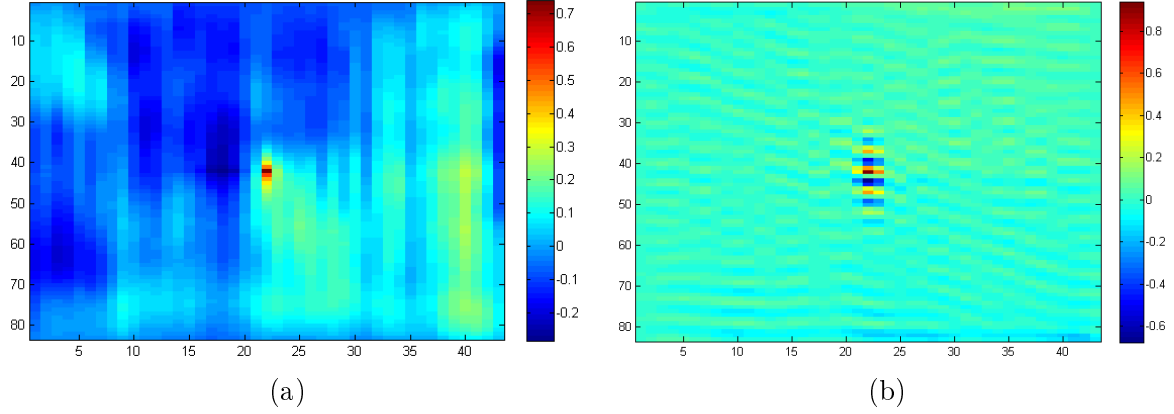


Figure 3.11: (a) Example of NCC cost map of small block (7x11pixels) of ultrasound signal envelope compared to the surrounding signal envelope in next frame of the sequence. (b) Example of NCC cost map of small block (7x11pixels) of ultrasound RF signal compared to the surrounding RF signal in the next frame of the sequence. The maximum NCC is stronger than with the envelope alone, although there are more local maxima due to the signal peaks and troughs.

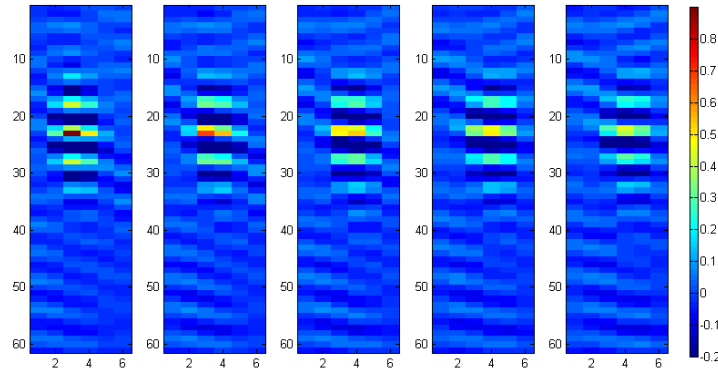


Figure 3.12: Progression of NCC cost maps as tissue is compressed between 1 and 5 frames (left to right). The maximum NCC moves upward (toward the probe in sub-pixel quantities) but decreases in value as the signals become more dissimilar to those in frame 1. Note that no signal or cost map upsampling has been applied to these figures.

Numerical methods such as the Levenberg-Marquardt algorithm [142] (a Newton method for non-linear responses with improved stability) can alternatively be used. Here, the displacement is a variable and an initial estimate is required and the algorithm adjusts and iteratively updates until an optimisation criterion is reached (such as minimum error, minimum error change or maximum number of iterations). The cost can be analysed at either the discrete points or by creating an interpolation function of one signal [143–145].

Each approach has advantages and disadvantages: the comprehensive search will become increasingly computationally expensive with larger block sizes and areas, but will add insights to the algorithm designer on the dynamics of the cost map. Conversely, numerical methods risk finding a local minimum/maximum that is not the true solution and can be slower than a comprehensive if the minimisation criteria are improperly set. These considerations can be implied from figure 3.12, where the effect of larger displacements can be seen to decrease the NCC value and the global maximum becomes less distinct from nearby maxima.

Cost functions have been compared by individual groups and tend to conclude that SSD provide the best results (particularly for small window sizes) [146, 147] or that NCC results are comparable when performing 2D motion estimation using RF signal data [148].

Blocks are usually assessed somewhat sparsely - that there is little benefit of assessing every sample point as a block centre, and either block overlap percentages or centre spacings are quoted.

3.6.5 Assessing 2D strain from 2D displacement

Once the motion has been assessed from all defined block positions, a displacement field has been generated. The local gradient of the displacement field then provides strain estimates [149], which can be assessed discretely by the difference of successive points (equation 3.13, figure 3.13), or by finding the average strain over a set window of points. This can then be applied over each line of an image and used to construct a colour mapped image of axial displacement and strain (figure 3.14).

$$\frac{\partial u}{\partial x}(i) = \frac{d_{i+1} - d_i}{\delta x}, \quad (3.13)$$

$$= \frac{1}{(2W + 1)\delta x} \sum_{a=-W}^W d_{i+a} \quad (3.14)$$

where u is the displacement per unit frame time, W is the width of the averaging window, δx is the sample interval size (or pixel centre spacing).

The choice of W will affect the local point value of strain estimated as it will have a

smoothing effect. Larger windows cause smaller maximum strain values and decrease the effective resolution, with more blurring on strain boundaries. Where there is a significant amount of precision error in the initial displacement field however, this may work to improve image quality and decrease the impact of localised strain errors. Errors in strain values due to precision in the displacement field can be further reduced by delineating a region of interest (ROI) where the tissue is assumed to be homogeneous and subjected to similar external forces. By taking a mean value of strain in this region, the local variation of strain values can be reduced for comparison with other image acquisitions.

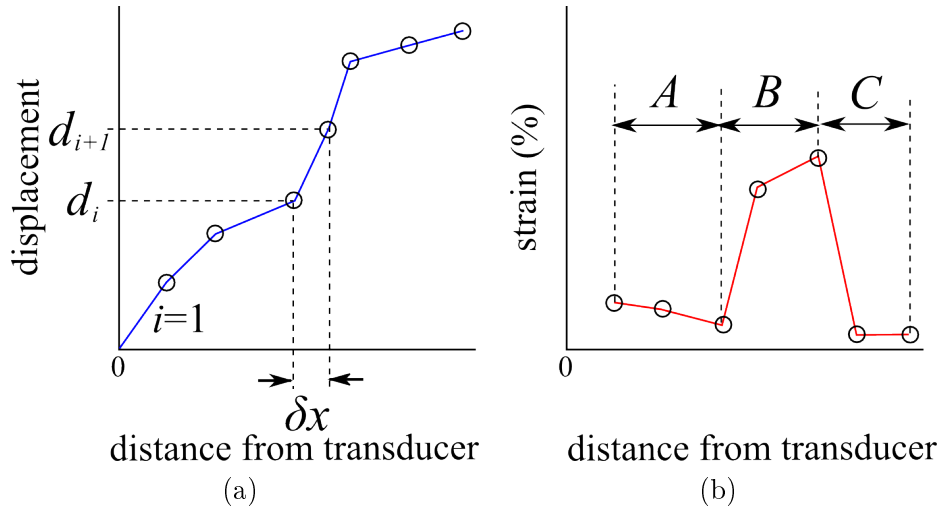


Figure 3.13: (a) Example 1D displacements. (b) Example 1D strains. Sections A and C have low strains while section B has a much higher strain.

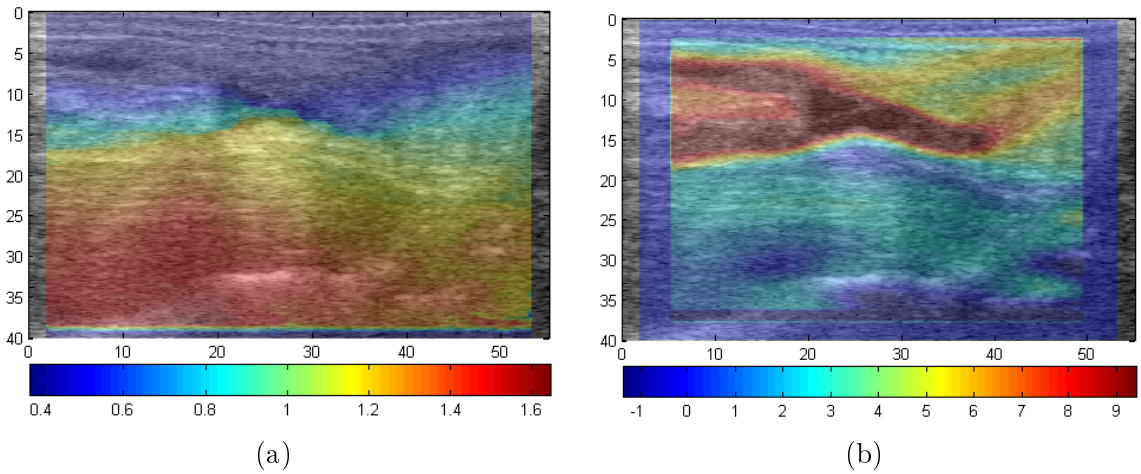


Figure 3.14: Example of (a) Axial displacement (mm) and (b) Axial strain (%) found over a 2D image sequence where the tissue is compressed.

3.7 Clinical use of axial elastography in tendons

The majority of elastography studies for Achilles tendon are medical studies using axial elastography available in commercial ultrasound systems. Elastography has first gained popularity as an alternative to assessment by palpation to examine a patient and has perceived advantages in being more sensitive, more capable of assessing deep tissue, less observer dependent, more comparable to other imaging modalities and can be easily documented or shared [150]. Commercially available compression elastography usually does not involve a large motion and often relies on the natural small movements inherent in holding the probe in contact with the skin. Most published literature regarding elastography in tendons comes from the medical community and regards assessing commercial systems as to their repeatability and sensitivity to changes of the images produced [151, 152].

Drakonaki et al. have used commercially available elastography to compare the strain patterns from 50 healthy (asymptomatic) Achilles tendons in the transverse and sagittal (longitudinal) image planes [153]. Their key parameter was a strain index found from the ratio of the strain in the free Achilles tendon and the Krager's fat pad (directly beneath the Achilles tendon) which was assessed with three repeat measurements by two radiologists with additional care to ensure that somewhat repeatable compression was applied. They found that the appearance of the strain images could vary between 'green and blue, with no evidence of red areas' to 'green with red stripes parallel to its long axis' but that this appearance was consistent on repeated image acquisitions for the sagittal plane. Images in the transverse plane were less consistent and they found no correlation of the two appearance groups with gender or age. For strain index measurements, intra-observer correlation coefficients were no higher than 0.78, with a coefficient of variation of 30.5%. Inter-observer correlation coefficients were much lower at 0.51, indicating that the measurements agreed approximately half the time. They also reported inconsistencies of the fat appearing more stiff than the tendon, and noted that the fat lies underneath the tendon and this may disrupt the consistency of the force applied. Similar qualitative results are reported by De Zordo et al. although without assessment of inter-observer effectiveness [154].

Tan et al. made observations of the appearance of elastography images in amateur

football players in 19 surgically repaired and 40 healthy Achilles tendons [155]. They assessed tendons at proximal, mid and distal sections and divided results between three groups of elastography image colour response and three assessments of homogeneity of colours. In healthy subjects they found no statistical difference between mid and distal portions, and these sections were more likely to be homogeneous than the proximal portion (away from the calcaneus and closer to the muscles). In the mid and distal sections they also found a statistically significant appearance difference between the ruptured and healthy tendons. However, they recognised that inter and intra-observer repeatability was not assessed and that results were not confirmed with comparison to histology.

More recently, Porta et al. performed a similar analysis to assess reproducibility of elastography images for 22 healthy patella tendons [156]. They found greater intra-observer repeatability ($0.613 < P < 0.865$ for various measures) and inter-observer agreement of $P=0.657$. They found that their images showed the patella tendon to be relatively elastic when compared to surrounding tissue, which was different to elastography observations from the Achilles. They concluded that elastography was a potentially useful tool, even though sensitivity to changes in the tissue had not been observed.

Klauser et al. have shown that compression elastography showed good agreement with histology in the case of tendon tears and that it was somewhat more sensitive than appearance of B-mode images alone [157].

3.8 Instantaneous elastography

There are several techniques used to provide an alternative to palpation in order to impart a stress on the tissue in the field-of-view and then view the resultant strain.

Acoustic radiation force impulse (ARFI) [158], **shear wave elastography** and **transient** (or vibrational) elastography are methods that generate a lateral shear wave. This shear wave propagates at low speeds but attenuates quickly. It is then tracked using conventional amplitude diagnostic ultrasound imaging. The speed of the shear wave is related to the local mechanical properties of the tissue [159] in the same way as previously described for MRE. In shear wave and ARFI imaging the shear wave is produced by ultrasound waves, whereas in transient elastography it is produced mechanically [160].

Shear wave imaging in particular has been trialled for measuring tendon properties [161, 162] as well as for muscles [163]. Brum et al. found elasticity modulus values in healthy Achilles tendons *in vivo* in the range 400-1300kPa in 5 subjects [161]; Aubury et al. reported Young's modulus values of 779.5 ± 57.1 kPa in 80 subjects [162]. However, most *in vivo* and *ex vivo* studies agree that the tensile Young's modulus should be approximately 0.5-1GPa [65]. Aubry et al. [162] and Brum et al. [161] both cited work by Kuo et al [66] as having similar values for elastic modulus, but Kuo et al. obtained their values by compression of tendon tissue rather than by tension, which may explain the difference in properties found. This may also indicate that the shear wave method does not stimulate strains that are suitable for characterising the functionally important properties of the tendon. The technique continues to be of interest and is investigated as to its ability to detect small, local tendon tears in *ex vivo* tendon models [164] and has been shown to distinguish newly ruptured from healthy tendon [165]. Chen et al. found healthy Achilles tendons to have elastic modulus of 291.9 ± 4.4 kPa (from 35 subjects) and ruptured tendons with a substantially lower elastic modulus at 56.48 ± 68.59 kPa (from 14 subjects). Although there was a clear difference ($P=0.006$) of healthy and rupture groups, it also has to be noted that the values for the healthy group are substantially different to those found by Brum et al. and Aubury et al., which draws into question the repeatability of this method between different research groups.

3.9 Lateral elastography

Konofagou et al. noted that estimating strain from axial direction compression alone resulted in major errors occurring from motion in the lateral and elevation directions [117]. Tracking of the RF signal was established to provide superior accuracy than signal envelope tracking [117, 122, 166–168] and interpolation of RF signals in the lateral direction was found to be possible as long as there is sufficient overlap of the beam paths [117]. Linear interpolation was used for the lateral direction. Konofagou et al. extended this to include signal “companding” in both directions, where the expected compression is synthetically imposed into the prior-signal in order to obtain a better match accuracy [169].

In the Konofagou implementation, signal correlation was applied to each of the axial and lateral directions independently as an iterative process. This algorithm was tested on synthesised ultrasound (5MHz central frequency) images of a homogeneous material compressed by known amounts and with a physical experiment of a gelatine phantom compressed axially by 1%. They concluded that use of lateral tracking could improve axial strain field quality (particularly for high strains), generate meaningful lateral strain fields that could gain insights and be used to generate meaningful Poisson ratio images.

Kaluzynski et al. performed a similar implementation without signal companding [135] using an annular phantom intended to simulate the cardiac wall. They made use of a tissue incompressibility assumption ($\varepsilon_x = -\varepsilon_y$) to produce reduced noise lateral elastograms as described by Lubinski et al. [170]. Here, they postulated that error in lateral tracking can be improved by taking the displacement values found from block matching and subtracting an error term from the axial strain field over an arbitrary window:

$$u_{LS}(n_0, m_0) = \frac{1}{2M+1} \left[\sum_{k=-M}^M u_m(n_0 + k, m_0) \right] - \frac{1}{2M+1} \left[\Delta \sum_{k=-M}^M \sum_{n'=0}^k -\varepsilon_y(n_0 + n', m_o) \right] \quad (3.15)$$

where u_{LS} is the updated lateral displacement estimate, M is the window size parameter, u_m is the original displacement estimate from block matching and ε_y is the axial strain.

This may work for small axial compression motions and strains in relatively homogeneous tissue where motion can be expected to be relatively planar, with small shear and with lateral/axial compressions well related to each other. In a more mechanically complex, multi-tissue field with large motion, initial experiments conducted by this author indicated that it had little benefit beyond smoothing the displacement field.

Revell et al. [139] and Chernak et al. [168, 171] presented the most directly relevant methods: both present imaging methods for lateral strain imaging as well as quantitative methods for assessing the accuracy of displacement tracking and strain quantities.

Revell et al. [139] presented a block matching method that used both NCC and CD_2 (a correlation of Rayleigh distributions in order to reduce noise) costs of the Fourier domain of the RF signal in a multiscale approach to track displacements. Accuracy of the motion sequence was enhanced using *drift updating*, a method where the cumulative displacements

($d_{cum} = d_{frame1,2} + d_{frame2,3} \dots d_{framen,n+1} + \dots d_{frameN-1,N}$) were updated by the high correlation estimates found by comparison of the n th frame to the first ($d_{ref} = d_{1,n}$) from the lowest resolution image scale. Drift updating was shown by Revell et al. to increase accuracy over large image sequences [139], although the precise implementation was not described in detail, which is significant as large frame intervals will have areas of low correlation which need to be discounted. The block matching method was validated in gelatine models (known as ‘phantoms’), *ex vivo* porcine tendons and *in vivo* examples of human Achilles and patella tendons. They concluded that block matching of tendons under strain could be used to accurately measure strains *in vivo* which could help identify tendon conditions although notably they did not note of the changes to ultrasound images of pathological tendons or attempt to differentiate different subject groups according to strains measured.

Chernak et al. presented a mechanical set up for validation using *ex vivo* porcine tendons in a saline water bath and stretched with a horizontal mechanical test machine. Their block matching algorithm consisted of using NCC of the synthetic lateral-phase of the RF sequence, with quartic interpolation of the cost-map to enhance sub-pixel estimates. Displacement estimates with $NCC < 0.7$ were dismissed and the tracking algorithm was run of the forwards and reverse frame-sequence and a weighted average of both results was computed in order to minimise local errors [171]. Having successfully shown that mean displacements correlated with grip-to-grip separation, the local displacements from ultrasound tracking were subsequently validated with surface displacements found by digital image correlation (DIC) of an optical video image sequence [168]. The superior accuracy of RF domain over B-mode tracking was confirmed both for tendon and for a tendon mimicking phantom made from polyvinyl chloride-plastisol with glass beads to act as ultrasonic scatterers. They found improved results (greater accuracy, lower variation in displacement estimates) for the phantom results than with tendon.

3.10 Chapter conclusions

This chapter has described the technological motivation for image-lateral elastography for measuring strain in damaged or partially healed Achilles tendons. This chapter has:

- Reviewed alternative imaging modalities to establish the relative benefits of ultrasound imaging, being safety, high frame rate and tissue texture.
- Established the physical principals of diagnostic ultrasound imaging, particularly its anisotropic nature, and introducing the concepts of the RF signal, signal envelope and signal phase and the relationship between them.
- Shown the key B-mode image features of healthy, ruptured and partially healed Achilles tendons.
- Introduced to the principles of 1D and 2D axial and lateral elastography.
- Reviewed recent literature regarding elastography to assess Achilles tendons. This covered both clinical use of commercially available axial elastography and research activity into lateral elastography for *in vivo*, *ex vivo* and phantom experiments.

This chapter has demonstrated that there is a significant interest in using and improving lateral elastography of the Achilles tendon for research and clinical applications. There is also an apparent lack of recognition of impact on the ultrasound images that can occur when viewing a ruptured tendon. The difficulties caused by these imaging features need to be assessed and tackled in order to progress the field. To this end, the original and novel contributions of this thesis relate to the development of an improved 2D block matching algorithm, its optimisation for this application, its use in a clinical pilot study, an investigation into further improvements of post-process regularisation and assessment of the remaining artefacts so that they can be further mitigated or addressed by future elastography systems.

Chapter 4

The AutoQual method of lateral elastography for quantitative assessment of ruptured Achilles tendons *in vivo*

4.1 Introduction and summary

The previous chapters have described the clinical and research desire to monitor mechanical properties of Achilles tendons in both healthy and post-rupture states and described the existing methods and technological considerations for measuring strain via ultrasound elastography.

This chapter describes the development and validation of a new elastography algorithm comprising several features and innovations that has been named ‘AutoQual’ and which is used in subsequent chapters. This chapter represents an extended version of the paper ‘*The AutoQual ultrasound elastography method for quantitative assessment of lateral strain in post rupture Achilles tendons*’ which has been published by the Journal of Biomechanics [172], with additional explanation of the elastography method.

4.2 Motivation

4.2.1 In vivo strain measurement of tendons

As previously discussed, there is a strong desire to measure mechanical properties of tendons *in vivo*, with expectation that they will provide an objective and quantitative method for assessing tendon function. Most existing methods for assessing tensile strain in the Achilles tendon track motion of ultrasound image sequences using a small number of points (usually a single one) linked to significant anatomical features such as the the muscle-tendon junction (MTJ, also referred to as myotendinous junction) [57, 173] or free tendon substance [67]. These methods rely on the accuracy of tracking only these single/few points, do not target pathology and usually make assumptions on the motion

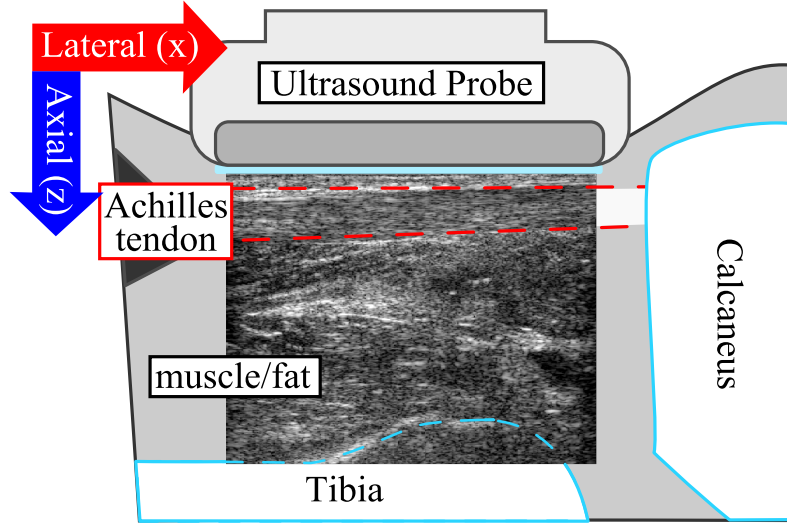


Figure 4.1: *Diagram showing the main features and axis of orientation in a typical longitudinal plane ultrasound image of a healthy Achilles tendon. Drawn structures not to scale (reproduction of figure 1.1).*

of the calcaneus (due to limited field of view of ultrasound probes) to infer the changes in total tendon length.

Most 2D image elastography methods focus on strain estimation fields found from compression of the tissue by small perturbations of the US probe against the subject's skin and not from tensile stretching along of the tendon which lies in the image-lateral direction (an example of a sagittal-plane B-mode image of a healthy Achilles tendon with axes defined as used is shown in figure 4.1). The anisotropic nature of the Achilles also needs to be considered: its functional properties are principally defined in the tissue's longitudinal direction and thus changes in material properties due to changes in the tendon's substructure cannot be expected to be found by compression that is perpendicular to the fibre direction.

4.2.2 Difficulties in ultrasound block tracking for tendons

Block tracking of displacements in the image-lateral direction is more difficult than in the signal direction due to 3-5 times lower spatial resolution and reduced continuity of the signal across different US scanning lines. Deliberately manipulating the tissue in the image-lateral direction also adds to the problems. The influence of reflections and shadows affects deeper tissue particularly and there is an increased potential for out of plane motion from different tissue structures compared with signal-direction compression.

It is important to consider the image attributes for both healthy and pathological tissues being assessed. US images of healthy Achilles tendons have low contrast between tendons and surrounding tissue and have no distinct local image features. The tendon tissue can be identified by the image texture from its fibrillar structure and by flexion of the foot causing motion that allows the structure to be more clearly delineated. Tendons can become inflamed when damaged, increasing in size from approximately 5mm deep to 10-20mm thick and ultrasound images of tendons appear darker due to increased water content and decreased US reflective planes (similar changes can also occur for non-rupture tendinopathies). It is, however, possible for tendons to exhibit tissue degradation, lesions, and cause pain without inflammation being present [174–176]. Ultrasound image texture usually changes too, with randomly orientated fibres and blood clots that may absorb signal to cause shadows. Where surgical treatment has been applied, the suture can disrupt the texture and cause shadows.

These factors can have significant impact upon multiscale block matching algorithms, as poor correlation between US frames at any scale lead to erroneous estimations of displacement over potentially large regions, which tend also be close to the rupture site. This results in discontinuities in the calculated displacement fields as well as misleading image artefacts and erroneous quantities in the strain field images.

4.2.3 Clinical measures and mechanical properties

Detailed and accurate biomechanical information about tendons *in vivo* is difficult to obtain, with poor specificity in obvious symptoms, as well as uncertainty and lack of quantification in visible signs of tissue degradation or of repair. Current clinical functional measures are largely limited to subjective questionnaires on pain response and movement restriction [44]. Measurement of mechanical properties could provide a more objective measure of tendon health.

A method that can quantitatively and repeatably measure biomechanical properties would provide new insights into the healing process, with the possibilities of being utilised for diagnosis of conditions before they become acute or chronic.

4.3 Aims

Multiscale methods for measuring tendon strain post-rupture have previously been used by this group [177, 178] but are vulnerable to show discontinuities, particularly in areas of low signal strength. This chapter proposes a new US elastography method that is more appropriate for measuring image-lateral strain *in vivo* in damaged Achilles tendons. The aims are to:

- Describe the elements of the innovative ‘AutoQual’ method.
- Present experimental methods for comparing algorithms using phantom block and
- Qualitatively demonstrate clinical examples where the AutoQual method reduces errors found by MS elastography for recently ruptured Achilles tendons.

4.4 Methods

The AutoQual block matching method incorporates several elements that enhance robustness and repeatability, improve the continuity of strain and displacement images, decrease the error of the calculated displacement field, increase the displacement field-of-view size and reduce the dependence on user specified search regions compared to multiscale block matching method.

AutoQual is a single RF-signal scale block matching algorithm using the Quality Determined Search (QDS) method [179] and bicubic spline interpolation of the RF signal [144]. In addition, novel adaptive block size (ABS) and automatic search range (ASR) components have been included to greatly improve the capabilities and robustness of the block matching .

This new method is compared to a more conventional MS approach. This has many components in common with the AutoQual method, allowing direct comparison of the innovative features. A flow diagram illustrating the principal calculation stages for the basic MS algorithm is shown in figure 4.2 for reference. Here, each frame is treated as an independent ‘pre’

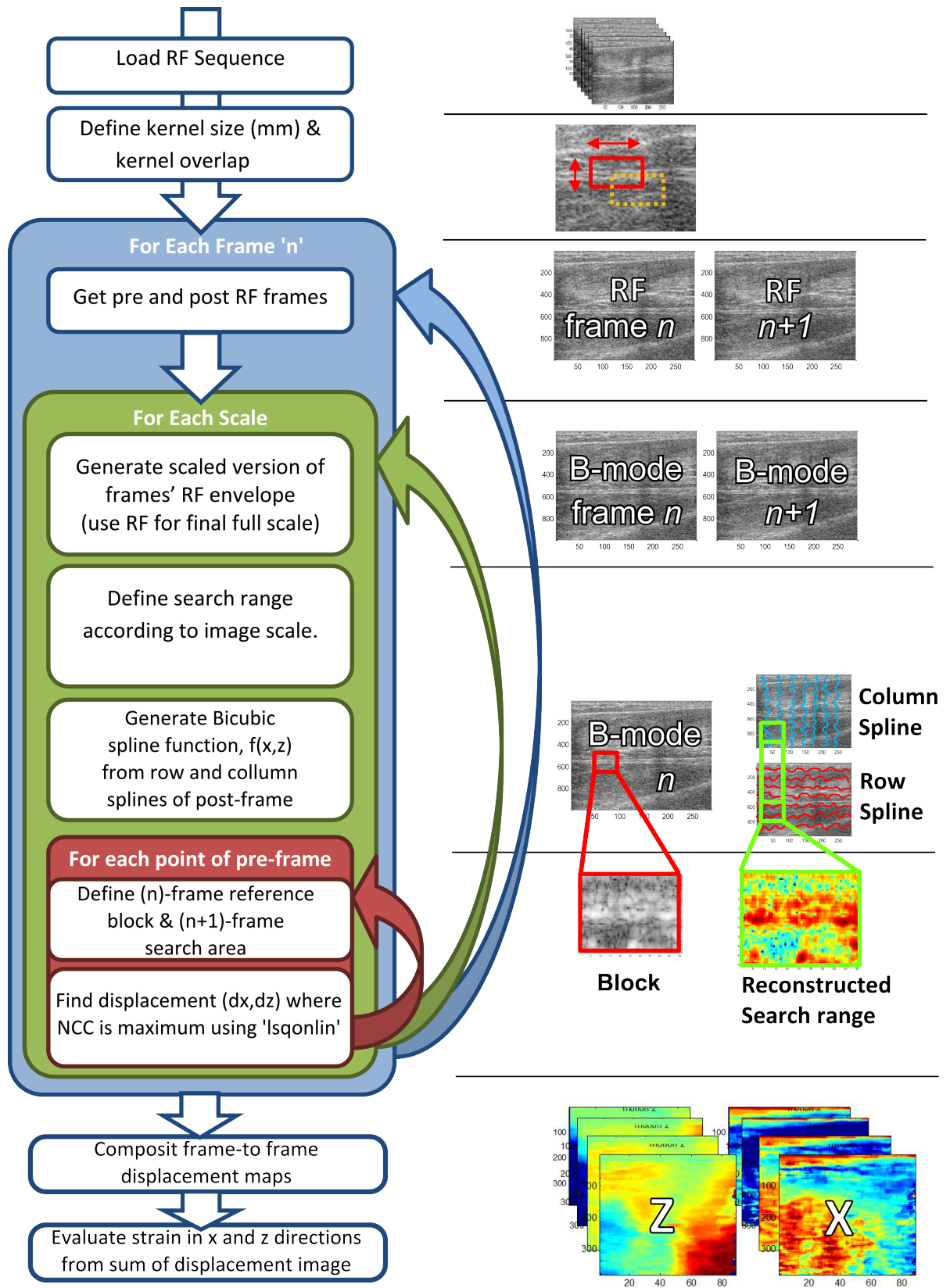


Figure 4.2: Flow diagram showing the principal stages in block matching algorithms used in this chapter.

4.4.1 Components of the AutoQual method

4.4.1.1 *Quality Determined Search*

The QDS method [179] allows arrays of block matching estimates to be treated as dependent on each other. The displacement of an initial small sub-set of ‘seed’ blocks is evaluated, then the neighbouring blocks to those with the best correlation are evaluated next with the value of the parent seed block used as an initial estimate. The process is then repeated with the results being cascaded from areas of good correlation into the areas of low correlation. As with the later published ‘hybrid’ method by Chen et al. [180] this QDS implementation is initiated with a small number (5-9) of seed blocks calculated by a MS approach similar to that described for the purely MS method in section 4.4.2.1 in the top 10% of the image where signal quality is the greatest but far enough away from the transducer to avoid near field effects.

4.4.1.2 *Automatic Search Range*

Conventionally, a block matching search range is set arbitrarily and centred around the original position of the image block being matched. However, with the quality determined search, an initial, non-zero, estimate of the displacement is given. By automatically searching in a defined region around this initial estimate, smaller search regions can be used. This also reduces the requirement for a user to specify larger search ranges when a large motion is expected (which leads to increased noise and error) due to continuity within the tissue motion allowing initial estimates to gradually propagate along a displacement gradient. Reducing the search range has the additional benefit of reducing the computational effort required (although this is not an objective of this work) and limiting the potential discontinuity between blocks.

In the phantom block experiments and the *in vivo* examples, an automatic search range is implemented of ± 5 pixels (0.077mm) in the z-direction and ± 1 pixel (0.149mm) in the x-direction. This adds extra, but informed, restrictions to the displacement tracking by preserving continuity and similarity to neighbouring estimates rather than finding the best NCC maxima over a large search range. This is of particular use in areas with low signal strength, low texture or out of plane motion, where the greatest global correlation

may not be the most accurate estimate. A similar automatic search range could be used in MS approaches but will not have the benefit of reinforcing the continuity of displacement estimates that is implied by the QDS method. It should be noted that for faster motion or very high strains this could be considered as an over restriction, but this is relaxed by the use of the Adaptive Block Size strategy, described next.

4.4.1.3 Adaptive Block Size

One of the problems with block matching algorithms is the effect on the image edges and overly rigid constraint from a limited search range. The area where a cost function can be accurately mapped is limited as any material that leaves the field of view of the US probe cannot be matched to the correct place of the previous frame, thus an erroneous maxima of the NCC cost function may be found. This is particularly a problem when large block sizes are used as relatively small amounts of material leaving the field of view can have large consequences on the displacement estimate. Adaptive Block Size (ABS) allows the search algorithm to use smaller windows when at the edge of the specified search region. This allows more continuous displacement fields to be generated around the image edges and makes the algorithm more robust by being less dependent on user specified search ranges as displacements larger than the search range can be found. As part of the numerical search method employed, the block size is defined as:

$$Xmin = \max([1; i - B_x - 1])$$

$$Xmax = \min([S_x; i + B_x])$$

$$Zmin = \max([1; k - B_z - 1])$$

$$Zmax = \min([S_z; k + B_z]) \tag{4.1}$$

Where S is the size of the search region, B is half the block size (assumed odd, rounded down) and X and Z are the coordinate ranges used to define the interpolated 2D signal to be compared.

The Automatic Search Range and Adaptive Block Size strategies are summarised in

figure 4.3.

It should be noted that the Adaptive Block Size strategy is not a competing design choice against a multiscale approach: multiscale searching could be carried out in conjunction with ABS. However, in initial testing it was found that little or no qualitative advantage was gained when using multiscale searching with the QDS and ASR features and so this combination is not implemented here.

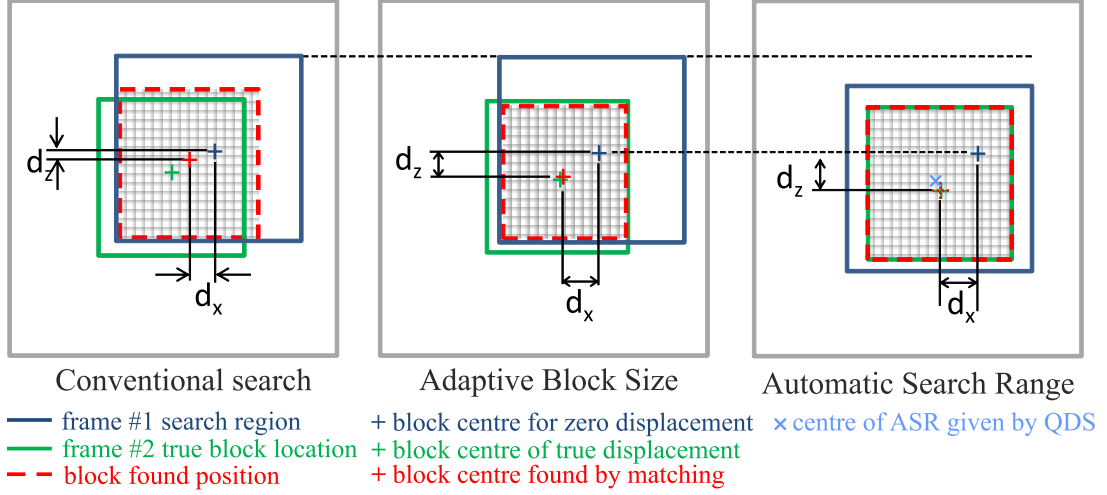


Figure 4.3: Summary of conventional zero-centred search range, Adaptive Block Size and Automatic Search Range strategies. Shown is a large displacement that could not be expected to be found within the conventional search range (green +). The best a conventional search can find is at the edge of the search region, and may find a local maximum correlation at any point in the search region. Adaptive block size allows smaller blocks to be used at the edge of the search range and thus relaxes the boundary and allows larger displacements to be found. Automatic search range helps ensure that the search area will be selected the target area is likely to be included in the search range.

4.4.2 Components of the Multiscale method

4.4.2.1 2D Multiscale block matching

Tracking of tissue is most accurately achieved by correlation of signals at the finest imaging level (RF signal), provided that there is a good initialisation. As the cost function is complicated there are many local maxima of correlation. At coarser scales (B-mode greyscale) the general motion of material is more visibly obvious, but obtaining a fine degree of accuracy is more difficult as information has been lost and resolution is lower. Making an initial estimate at lower scales and then progressively initialising higher scales of block matching is a method that combines the ability of low-scale matching to capture

large movements and of high-scales to refine the accuracy.

The Multiscale method used here performs block matching first at $\frac{1}{4}$ scale of RF resolution using non-log compressed signal envelope, then at $\frac{1}{2}$ scale, and finally using the RF signal.

4.4.2.2 Search range for multiscale block matching

A much wider search range must be used for an origin-centred search in order to make it capable of tracking displacements at all depths and for all reasonably expected material displacement speeds. This is because it does not allow information from adjacent pixel estimates to affect new estimates (unless through post estimation regularization or if searches are performed iteratively). In this implementation the search range is not tailored to the specific experiments, but instead uses values based upon experience from *in vivo* image sequences. The values used are +/- 30 pixels (0.4621mm) in the z-direction and +/- 2 pixels (0.30mm) in the x-direction.

4.4.3 Components in both Multiscale and AutoQual methods

4.4.3.1 2D Bicubic Spline Interpolation

The method uses non-separable 2D bicubic spline interpolation of the RF signal as described in [144] to allow for sub pixel tracking. Here, 2D functions of the signal in x and z are inferred from the original signals and used to infer values at spatial positions different to those captured by the discrete sampling of the ultrasound imaging hardware. This functional version of one of the signal spaces being compared can be then used to obtain a more accurate estimate of the displacements found between frames as described below.

If the bicubic spline is a cubic function of x and z defined between nodal points at each pixel (i and k respectively), then the value of any point can be described by equation 4.2 [181].

$$f_{i,k}(x, z) = \sum_{p=0}^3 \sum_{q=0}^3 \kappa_{pq} x^p z^q \quad (4.2)$$

where $0 \leq x \leq 1$, $0 \leq z \leq 1$ To evaluate the bicubic coefficients κ , 1D spline functions in the x-direction are evaluated at $z=0$, $z=0.5$, $z=1$ and in the z-direction at $x=0$, $x=0.5$ and $x=1$ in the form shown in equation 4.3, where ${}_n\alpha$ are the spline coefficients.

$$f(x, 0) = {}_0\alpha_{i,k} + {}_1\alpha_{i,k}x + {}_2\alpha_{i,k}x^2 + {}_3\alpha_{i,k}x^3 \quad (4.3)$$

The orthogonal 1D spline coefficients are then equated to the similar coefficients in the bicubic equation to obtain 14 simultaneous equations plus the point values of the original image (disregarding the highest order term in the bicubic). This is demonstrated in the matrix of coefficients shown in equation 4.4. These can be efficiently solved for the whole image to evaluate the 2D bicubic spline coefficients, and blocks of the coefficients used and evaluated at interpolated points when required.

$$\begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1/2 & 0 & 0 & 0 & 1/4 & 0 & 1/8 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1/2 & 0 & 0 & 1/4 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1/2 & 0 & 0 & 1/4 \end{bmatrix} \begin{bmatrix} {}_{00}\kappa_{i,k} \\ {}_{01}\kappa_{i,k} \\ {}_{10}\kappa_{i,k} \\ {}_{02}\kappa_{i,k} \\ {}_{20}\kappa_{i,k} \\ {}_{11}\kappa_{i,k} \\ {}_{03}\kappa_{i,k} \\ {}_{30}\kappa_{i,k} \\ {}_{12}\kappa_{i,k} \\ {}_{21}\kappa_{i,k} \\ {}_{13}\kappa_{i,k} \\ {}_{31}\kappa_{i,k} \\ {}_{22}\kappa_{i,k} \\ {}_{23}\kappa_{i,k} \\ {}_{32}\kappa_{i,k} \end{bmatrix} = \begin{bmatrix} {}_0a_{i,k} \\ {}_1a_{i,k} \\ {}_2a_{i,k} \\ {}_3a_{i,k} \\ {}_1b_{i,k} \\ {}_2b_{i,k} \\ {}_3b_{i,k} \\ {}_1a_{i+1,k} \\ {}_2a_{i+1,k} \\ {}_3a_{i+1,k} \\ {}_2b_{i,k+1} \\ {}_3b_{i,k+1} \\ {}_2a_{i+0.5,k} \\ {}_3a_{i+0.5,k} \\ {}_3b_{i,k+0.5} \end{bmatrix} \quad (4.4)$$

where β are the spline coefficients from the z-direction splines. It should be noted that selecting the interval of exactly half way between the pixel values is arbitrary and that selection of a different value, or of evaluating splines in each direction based on even / odd pixels will have a similar end result and should only significantly affect the higher order terms in equation 4.4.

The 1D Spline coefficients were calculated with a continuous second derivative that allows overshoots as this was found this gave consistent results, whereas allowing non-smooth splines sometimes caused gross errors. The ‘not-a-knot’ condition (which specifies a continuous third derivative for penultimate and final points rather than a ‘natural’ condition of second derivative at zero) was also included for the spline periphery, although

this has negligible effects for the majority of the image. The cost is described as a continuous function in x and z Cartesian coordinates and solved numerically to find the local minimum.

For both AutoQual and MS methods a final RF resolution block size of 51x25 pixels z by x (equivalent to approximately 2mm x 4.75mm for this US probe) was used for block matching, except in instances where the Adaptive Block Size methods were applied in the AutoQual algorithm. This is a generic block size that has been empirically found to be acceptable for both block matching methods, and is within the range of reported block sizes as in [122]. The large block size in the x -direction enhances matching signals with lateral displacement while the smaller z -direction is required to reduce error around shearing boundaries expected between the tendon and deeper material. A relatively high level of block overlap was used with centres spaced by 15x2 pixels (depth by width).

4.4.3.2 Regularization

A 2D median filter has been used on each frame to frame displacement map in order to remove occasional outliers.

4.4.3.3 Multiframe displacement summation

The total displacement field for the sequence is found by composing the frame-to-frame displacement fields. In order to obtain a continuous point tracking, each displacement field frame is interpolated to find the values at the locations described by the sum of the previous displacements in the sequence. This is shown in equation 4.5.

$$D(i, k, n + 1) = D(i, k, n) + d(i + D_x(i, k, n), k + D_z(i, k, n), n + 1) \quad (4.5)$$

Where D is a matrix of cumulative displacements x and z directions relative to the original starting positions at frame n in and positions i and k ; D_x and D_z are the orthogonal components of D ; d is the non-cumulative frame-to-frame displacement field at frame n in and positions i and k .

This formulation accounts for the cumulative displacement (and strain) of tissue with time and with respect to the position of the 2D image in the initial frame. However, errors

will stack and errors in a single frame-to-frame displacement estimate can significantly impact the final image.

4.4.3.4 Strain imaging from the displacement image

The local strain for the entire motion sequence is estimated by taking the local displacement gradient. This is achieved by fitting linear trends weighted by the NCC in the axial and longitudinal directions for the axial and longitudinal displacement images (respectively) over small, overlapping, local 2D windows (figure 4.4). The value of the gradient is ascribed to the central sample position to build up strain maps in horizontal and vertical directions. The linear fit acts as an additional form of regularization to the displacement field, reducing the contribution of localised gradient steps. This does, however, add arbitrary smoothing and reduces peak strain values.

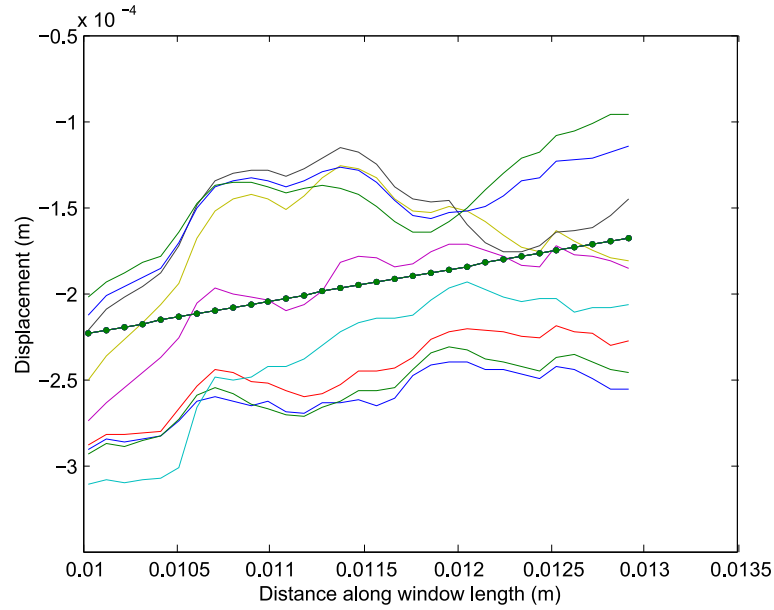


Figure 4.4: Example of a linear fit to a series of displacement points in the x -direction. Each curve represents a separate line of the the displacement image in the z -direction. The local strain of the central pixel of the strain window is given by the gradient of the linear fit.

4.4.4 Region of interest selection

Once the strain images have been generated, the region of interest was identified where the mean strain can be identified over in order to minimise localised precision errors (figure 4.5). In the case of rupture subjects this was notionally at the rupture zone. The region selected was as homogeneous as possible in terms of the strain field and the B-mode

image appearance. It is expected that variation and discontinuities in the displacement field could lead to non-homogeneous strain fields at the rupture zone, possibly leading to (erroneous) high-positive and high-negative strains in close proximity. This is further illustrated for a 1D example in figure 4.6. In these cases a suitably wide ROI is taken to reduce a large bias as the high negative and high positive strains will cancel out.

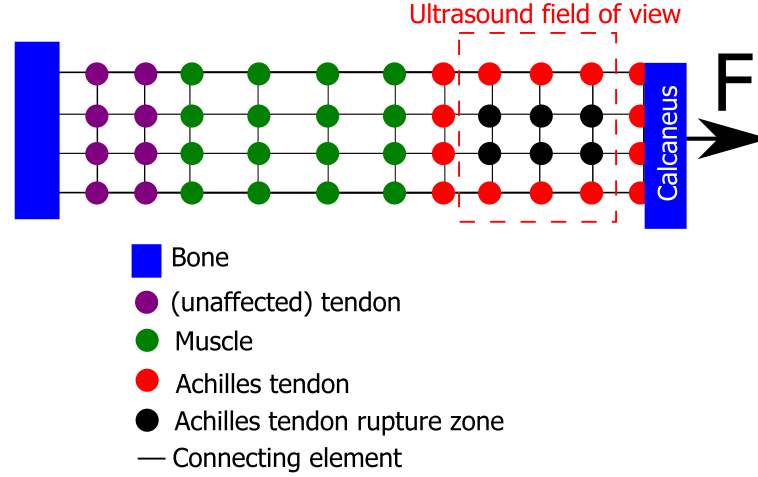


Figure 4.5: 2D mass spring model of the lower leg. As the force F is applied, a continuity of force is experienced along the horizontal connecting elements and the stiff ones will experience less deformation than the less stiff ones.

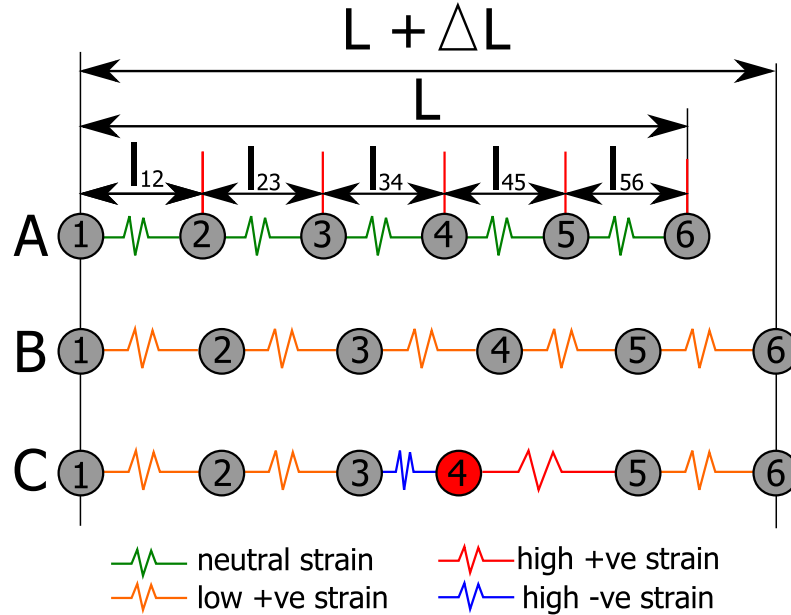


Figure 4.6: 1D example of ROI selection to mitigate local strain errors. Systems B and C are both stretched by the same amount, ΔL , which is equal to the sum of extensions of elements l . System C however, has an error in measurement of element 4, leading to local strain errors. The total strain for elements 1-6 is unaffected but the strain variation increases.

In this analysis this is conducted by manual selection and there is potential for erro-

neous selection.

4.5 Experiments

This experimental method for comparing the algorithms uses phantom block experiments with controlled motion to provide quantitative assessment as well as *in vivo* data from scans of four human subjects for checking qualitative performance. The ultrasound system was a Zonare z.one (ZONARE Medical Systems, Inc, Mountain View, CA) with a L14-5 linear transducer, central frequency 12MHz, frame rate 13.4Hz. Human data acquisition was approved by the Oxfordshire Ethics Committee B (reference 09/H0605/78) and registered at the International Standard Randomized Controlled Trial (ISRCTN93608625). It conformed with the current revision of the Declaration of Helsinki and ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

4.5.1 Method: Rigid body motion phantom tests

The phantom block used was a 80mm sided cube made of 5% agarose gelatin with talc powder to provide texture in the US image. The phantom was cast in a custom mould that allowed it to be clamped in a vertical mechanical testing machine (Zwick/Roell Z005) which provided ground truth for displacement and strain calculation. The US probe was mounted parallel to the direction of motion (figure 4.7(a)). A minimal contact gap and transmission gel assured good acoustic contact.

The phantom was displaced by 3.5mm (with zero strain) at set constant speeds in the range 1.0-5.0mm/s, representative of slow passive motion of the Achilles tendon. To minimize mechanical error (such as initial friction between the probe and the phantom) absolute error of the steady-state speed compared to the testing machine is reported rather than displacement error. Figure 4.7(b) shows a typical response of the average motion tracking response, which clearly shows a delay in the tracked speed compared to the actual speed of the phantom. Observation of the ultrasound images and of the test led to the conclusion that this error is not an error in the ability to track the image, but an error in the mechanical set up. Therefore, the steady-state speed (the mean average of the speeds of the plateau region in figure 4.7(b)) was compared to the speed that the

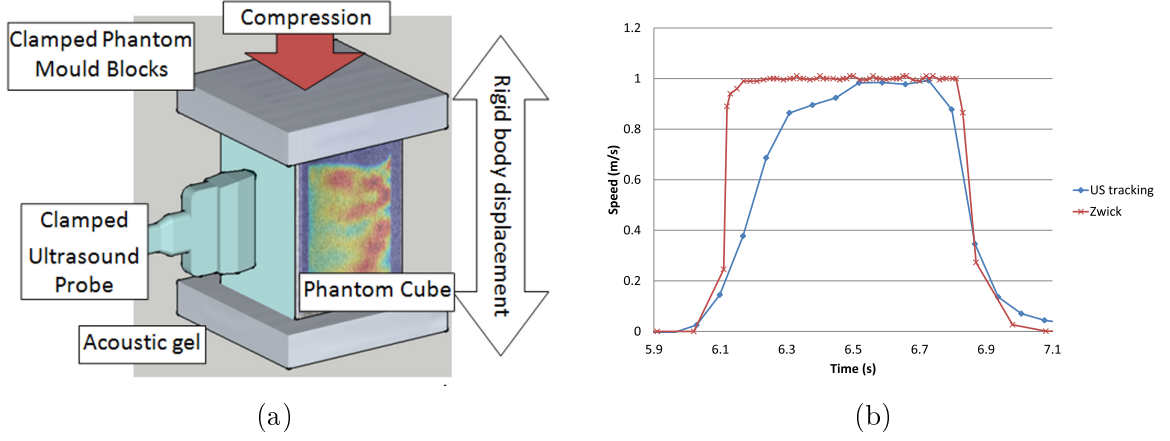


Figure 4.7: (a) Apparatus for phantom cube tests. (b) Typical instantaneous speeds for rigid body phantom tests from Zwick mechanical test machine and from block match tracking from ultrasound. This example from a 1mm/s speed moving a total of 0.75mm distance.

phantom moved. Three repeat measurements were taken for each speed and the probe was repositioned between each in order to reduce bias due to the probe angle.

4.5.2 Method: Controlled strain phantom tests

The same phantom block was used in these experiments as in the rigid body tests described in section 4.5.1. The first strain test attained a range of strains (1.25% - 4.38%) at a constant grip-to-grip speed of 1.5mm/s to report the normalized square error (NSE) from ground truth as shown in equation 4.6. The NSE was analyzed for the top 10mm depth of phantom block as is the typical depth for Achilles tendons and sequences were from decompression cycles to simulate elongation.

$$NSE = (\overline{\varepsilon_E} - \varepsilon_N)^2 / \varepsilon_N \quad (4.6)$$

where $\overline{\varepsilon_E}$ is the average strain computed by elastography and $\overline{\varepsilon_N}$ is the notional average strain based on the testing machine grip separation. The second strain test assessed the uniformity of the strain fields for a constant strain target of 4.38% (3.5mm decompression) and grip-to-grip speeds of 1.0-5.0mm/s. The standard deviation of strain was calculated from the two elastography algorithms. As a uniform strain is expected, higher standard deviations would indicate increased and undesired variability.

Subject	Subject description
A	Week 0 rupture, manual motion
B	Week 6 rupture, controlled motion
C	Healthy Tendon, controlled motion
D	Week 0 rupture, controlled motion

Table 4.1: *Key of subject descriptions for the four in vivo examples.*

4.5.3 Method: In vivo testing

Four *in vivo* sequences of Achilles tendons were acquired with controlled passive dorsiflexion from a force-neutral foot position (approximately 110°) and 1-5mm of tendon movement using either a motorized foot device or manual clinician manipulation (table 4.1). More details about the motorized foot device are included in chapter 6. The probe was held in contact with the subject by an experienced clinician. Passive motion has been shown to produce stiffness measurements that are highly correlated to those found by voluntary contraction [62] and was judged to be acceptable to subjects with recent ruptures as it would provide minimal pain or risk of further damage compared with weight bearing or voluntary muscle contractions and with more repeatable results. The sequences had both AutoQual and MS algorithms applied. Due to lack of ground truth, qualitative comments of the 2D tracking, average NCC over the region of interest as a matching quality metric and the standard deviation of strain as a noise descriptor are reported.

4.6 Results

4.6.1 Results: Rigid body motion phantom results

There were only small differences between the two methods in the errors of the steady-state speeds for the range investigated (figure 4.8). Both algorithms overestimated the steady-state speed for speeds of 1-2.5mm/s and underestimated for the 3.5-5mm/s tests. At higher speeds there is some indication that the MS method may give less consistent results than the AutoQual method with repeat experiments, as the results for the 4.5mm/s test in particular show a wider variation in results. The largest absolute error at 2mm/s gives approximately 2.5% displacement error over the sequence.

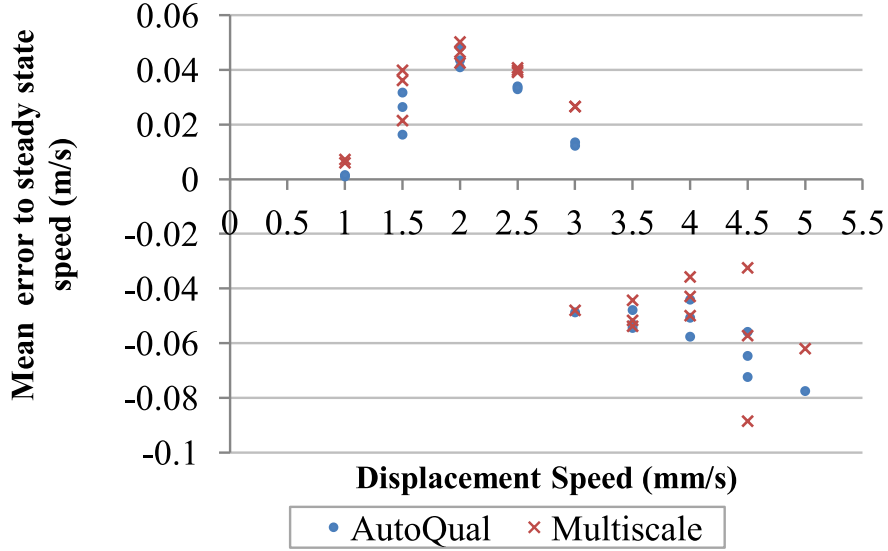


Figure 4.8: *Steady-state speed error in displaced phantom block for AutoQual and Multiscale methods*

4.6.2 Results: Controlled strain phantom tests

The AutoQual method showed substantially lower NSE values at all strains (Figure 4.9). The mean NSE for the AutoQual method was 1.22×10^{-3} compared with the MS method NSE of 2.41×10^{-3} .

The variability of the calculated strain fields at different compression speeds is shown in figure 4.10. The AutoQual and MS methods have similar uniformity of strain field speeds up to 4.0mm/s, but above this the MS method has less uniform strain fields than AutoQual.

4.6.3 Results: In vivo data

Figures 4.11(a) and 4.11(b) show a newly ruptured Achilles tendon subjected to passive ankle flexion by a few millimetres (subject A in table 4.1). The B-mode image (figure 4.11(b) *left*) clearly shows a large, hypoechoic region which is at the rupture zone (h). There is a clear displacement gradient in both of the displacement images (figures 4.11(a) & 4.11(b) *middle*) where the part of the tendon closest to the calcaneus (the right side of this image) moves more than the rest.

The MS displacement image (figure 4.11(a) *middle*) shows the sources of some of the artefacts in the strain image (figure 4.11(a) *right*). Points *p*, *q* and *r* all show local areas of discontinuities in the displacement field which, while small in size, are larger than a

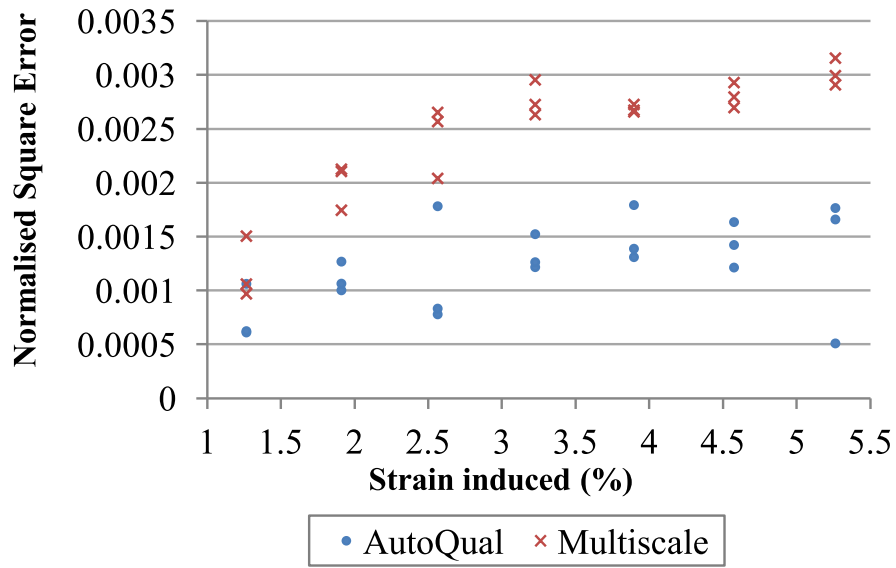


Figure 4.9: Normalised square error between elastography and ground truth strain on a phantom block at a grip-to-grip speed of 1.5mm/s for AutoQual and Multiscale methods

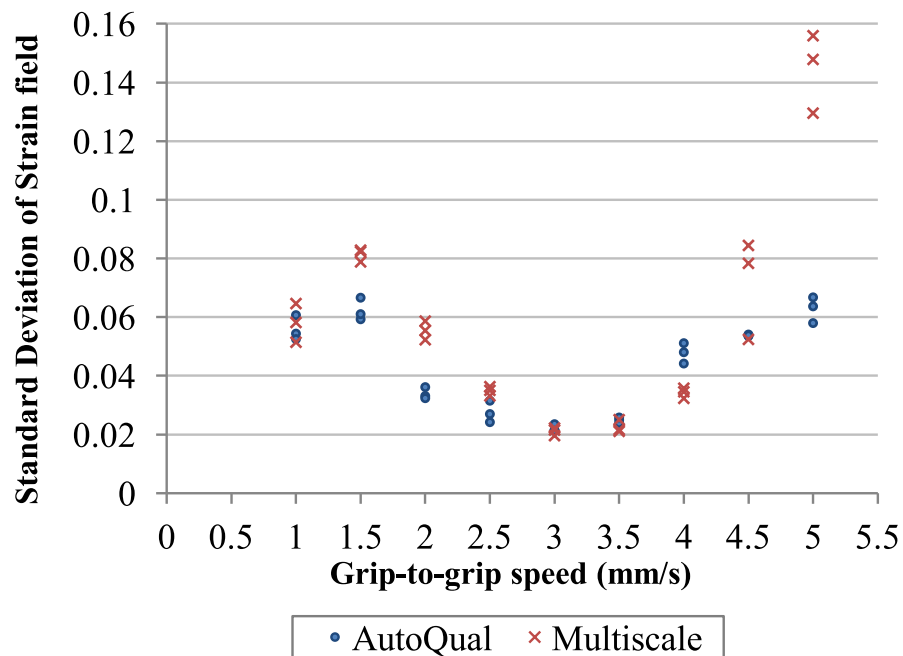


Figure 4.10: The standard deviation of lateral elastography strain fields from induced strains on a phantom block at various grip-to-grip speeds for AutoQual and Multiscale methods

Subject	AutoQual NCC	Multiscale NCC
A	0.8373	0.4656
B	0.9755	0.9376
C	0.9821	0.9483
D	0.9710	0.9371

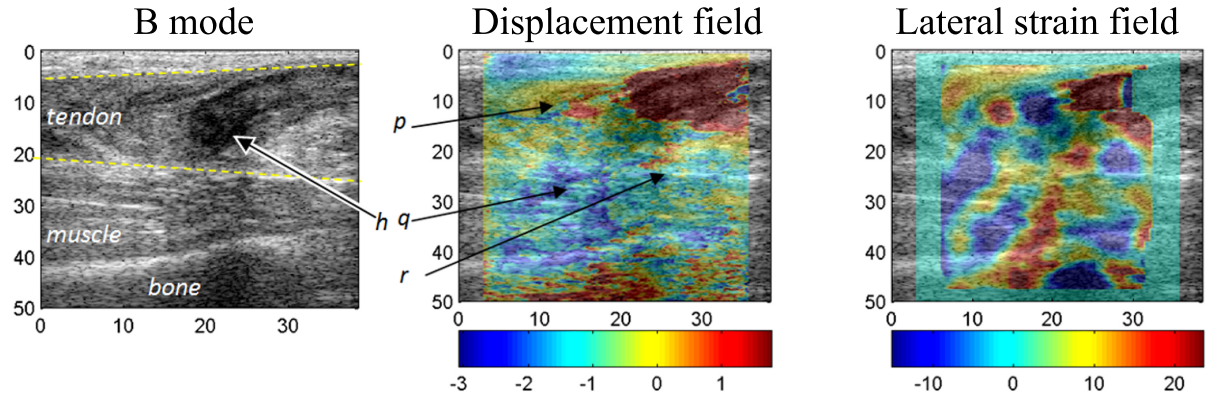
Table 4.2: *The average NCC found from the AutoQual and Multiscale block matching methods over the central or pathological area of four subjects undergoing passive motion of the Achilles tendons*

Subject	AutoQual σ	Multiscale σ
A	0.0990	0.2367
B	0.0157	0.0573
C	0.0158	0.0690
D	0.0501	0.0652

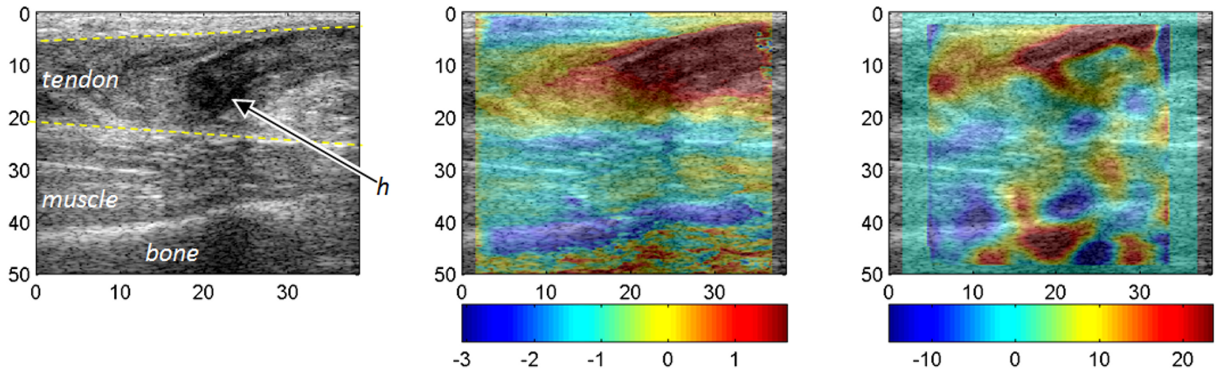
Table 4.3: *The standard deviation of strain values found from the AutoQual and Multiscale block matching methods over the central or pathological area of four subjects undergoing passive motion of the Achilles tendons*

general precision error. These are unlikely to be realistic representations of slippage in the tissue as a video representation of the displacement sequence appears to not correctly track the tissue. This could be caused by relatively small errors at lower resolutions of the MS method being propagated to higher scales and finding an incorrect NCC maxima or a decorrelation due to tissue rotation or poor acoustic transmission. The MS method is vulnerable to evaluating lateral displacements to discrete quantities, resulting in a defined edge rather than the steady gradient shown by the AutoQual method (figure 4.11(b) *middle*). Consequently, the AutoQual strain field (figure 4.11(b) *right*) is more uniform with a clear band of high strain across the blood clot boundary (*h*). The MS strain field is more confused, with alternating bands of negative and positive strain in all significant areas.

The AutoQual method consistently provides a higher NCC (greater correlation) than the MS method (Table 4.2) and the lower standard deviation of the strain field in the area of interest shows that the AutoQual method provides more consistent lateral strain measurements (Table 4.3).



(a) Example of Multiscale method applied to US image sequence of ruptured Achilles tendon.



(b) Example of AutoQual method applied to US image sequence of ruptured Achilles tendon.

Figure 4.11: Left: B-mode greyscale image of a recently ruptured Achilles tendon (subject A) from a foot flexion sequence. h shows the centre of the rupture zone. Middle: Displacement field (mm in x -direction). Noise and local high or low values at points p , q and r . Right: Lateral strain field. Local strain in % over 2×2 mm windows

4.7 Discussion

Quantitative evaluation of strain is difficult to achieve in a rigorous and repeatable manner *in vivo* and evaluating the performance of the methods designed to estimate these quantities is equally challenging. This report has demonstrated i) repeatable, relevant *in vitro* test methods using phantoms and tissue for elastography systems ii) increased quality of displacement estimates with a new AutoQual method and iii) The creation of standard data that can be used for benchmarking and further development of elastography algorithms. Importantly, the method of phantom rigid motion or strain acquisition can be readily achieved with a minimum of custom equipment and experience so should be repeatable by other groups.

Recent publications have been able to perform lateral tracking and local strain estimations on *ex vivo* tendons. The best examples that attempt to validate algorithms and performance are Chernak et al. [171] and Korstanje et al. [182]. However, their use of tissue alone for algorithm validation is not ideal. The possibility for variability in the tissue, difficulties of acoustic contact and gripping problems make this difficult to achieve or repeat and *in vivo* measurement lacks ground truth for comparison.

Korstanje et al. tracked rigid body motion and optimized the frame interval to minimize quantization error in their tracking algorithm. They measured error with an implanted US reflective marker within the *ex vivo* porcine or human cadaver tendon which was visually tracked by an observer. Their method was beneficial in that by using the whole cadaver acoustic contact between tissues is easily maintained and the tendon is inherently well anchored at the calcaneus (or animal equivalent). The reported relative error range was -2.2% to 4.4% (relative displacement); for AutoQual it is -1.6% to 2.3% (relative speed based on figure 4.8). The dynamics of the AutoQual algorithm are more accurately described at different speeds as is the accuracy at speeds typical of slow passive motion of a tendon or muscle, although Korstanje et al. were able to track displacements at speeds of up to 16mm/s. Based upon experience from human *in vivo* data, it can be seen that speeds of less than 5mm/s are appropriate and peak speeds from passive motion are unlikely to exceed this. Faster speeds may be appropriate for dynamic studies such as running or jumping. Rigid body tracking alone is, however, shown to not be a

sensitive test, as both the MS and AutoQual methods showed similar accuracies. It is notable that both algorithms showed overestimation initially and then underestimation of the steady-state speed (figure 4.8). Korstanje et al. made no comment on the ability to measure strain from their algorithm, and also only track a single region of interest (block) with little comment on the nature of noise in this tracking which can have a very substantial effect on local strain estimations.

The rigid body tracking experiment has highlighted an interesting feature of both AutoQual and MS algorithms: that they overestimate displacement at low speeds (up to 3mm/s) and underestimate it in the 3.5-5.0mm/s region. It has been calculated that the speed for exactly 1 pixel/frame for the Zonare ultrasound probe used is approximately 3.2mm/s - this could indicate that the algorithms experience an interpolation error or that there is a systematic error in the mechanical set up that has not been accounted for.

The work by Chernak et al. [171] performed strain analysis only. Their only validation of the displacement accuracy is to comment that the mid-section displacement of the *ex vivo* tendon is approximately a half of the grip-to-grip separation and that the average frame-to-frame displacements correlate well to a linear fit. There are no reported numerical values for displacement accuracy that can be compared to the work presented here. Chernak et al. reported strains at the mid section of the tendon which varied considerably, making it difficult to judge if the experiment was capable of validating the strain measured by their lateral elastography method. By contrast, the AutoQual phantom strain experiments have demonstrated similar and repeatable values with three repetitions at each different speed and different strain quantities, allowing a greater characterisation of the errors from the elastography methods.

The phantom block strain experiment more clearly shows the improved performance of the AutoQual method over the MS method. The strain fields showed similar levels of smoothness and uniformity and with a notably lesser deviation at grip-to-grip speeds above 4.0mm/s (Figure 4.10). At these higher speeds it is more likely that the MS algorithm will be unable to find a good correlation, and may find a local NCC maximum far away from the true value. This could happen over large areas that would not be improved upon by median filtering of the 2D displacement field. The AutoQual method's

QDS, ASR and ABS features means that even with decorrelated data it is unlikely that an erroneous discontinuous displacement will be found but retains flexibility to find other suitable displacements in the event of tissue slip in areas of good signal strength. The reduced size of the Automatic Search Range centred on the initial QDS means that even with decorrelated data it is unlikely that a better match in a discontinuous part of the image will be found. The Quality Determined Search provides reinforcement of values close to the already found good matches and disregards regions of poor frame-to-frame correlation until there is a large amount of superior displacement estimates to provide reinforcement. This led to less noise in the displacement field which was more effectively regularized by median filtering. The NSE for a range of strains was also shown to be consistently lower (Figure 4.9). This shows that the AutoQual method is consistently providing more accurate local lateral strain than the MS method. It is speculated that a similar trend would be seen for small local rotations as well as extension/compression, local out of plane motion and of areas of low signal strength; that local decorrelations will not disrupt continuity. These improvements would be consistent with those seen in the *in vivo* examples of the QDS in axial compression elastography from [180].

The phantom block experiment may show some mechanical response that introduces additional error into strain, which could be partially responsible for some of the behaviour seen. The main contribution is the bowing of the gelatine block's sides as it comes under compression. This occurs due to the Poisson's ratio expansion and may cause a more complicated strain field to be imparted than the spatially linear response expected (figure 4.12). Further improvements to the quantitative validation could be made by measuring the external dimensions of the phantom block at stages in the cycle and performing finite element analysis to corroborate local strain results.

These phantom experiments have conclusively shown that the AutoQual method is more accurate even in areas of good signal strength than a near equivalent MS method. It also shows that this simple experimental set up can be used to quantitatively distinguish between different algorithms performance in measuring image-lateral strain.

The *in vivo* data showed displacement and strain images that were qualitatively improved by the AutoQual method. The displacement and strain fields can also cover a

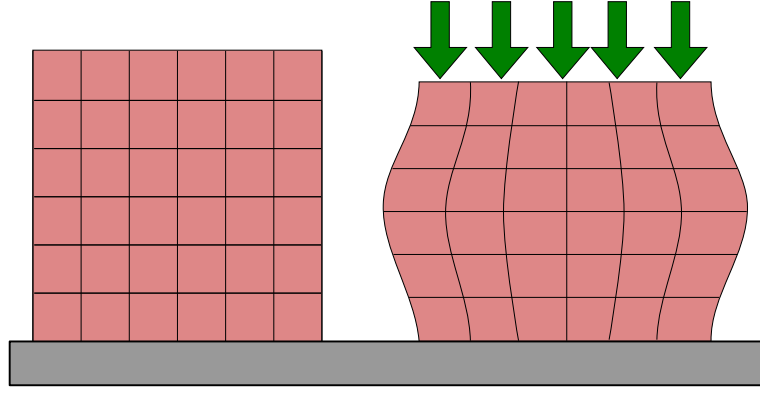


Figure 4.12: *Illustration of (exaggerated) Poisson's ratio expansion and bowing of phantom block sides that could occur and affect results.*

wider area due to the ABS capability. The edge noise from material leaving the field of view is also reduced with the AutoQual method. This additional field of view can aid the overall clinical perception. The edge effects from material leaving the field of view is also marginally reduced with the AutoQual method. The biggest improvements though, come directly at the rupture zone (point h in figure 4.11(b)), where low signal strength should lead to decorrelation, but continuity from the edges of the signal void provides, effectively, an interpolation across it.

While the Autoqual method shows notable improvement on these *in vivo* sequences, errors can still occur due to out of plane motion from the tissue motion, probe slip or loss of signal where the algorithm correctly tracks the image motion but that motion does not accurately represent the strains induced in the tissue.

Subject A shows areas of low signal, fast motion and material rotation, yet the AutoQual method provides visually credible results, a higher average NCC and a lower distribution of local strain values. The AutoQual block matching algorithm was more effective for subjects B, C and D also, despite slow motorized flexion leading to an improved performance of the MS method. In these scans the majority of the error in the MS evaluations could be tracked to a few frames (approximately one in ten frames) where these was either fast motion or an out of plane shift, leading to decorrelation. AutoQual was more able to cope with these factors and consistently lacked gross errors in the displacement field, despite having no temporal regularisation factor.

4.8 Chapter conclusions

This chapter has presented an innovative implementation of lateral ultrasound elastography *in vivo* for ruptured and partially healed Achilles tendons and simple, easily reproducible methods for testing such an algorithm. The innovations presented include:

- The first implementation of a Quality Determined Search algorithm for quantitative lateral elastography.
- The implementation of innovative Adaptive Block Size and Automatic Search Range concepts which compliment the QDS method and reduce the requirement to optimize search ranges.
- A simple, novel and repeatable experiment with a mechanical testing machine and a phantom block for quantifying rigid body lateral displacement error, lateral strain NSE and standard deviation.
- Demonstrating the AutoQual method is quantitatively superior to a multiscale method in the phantom block experiments.
- Demonstrating the AutoQual method is qualitatively superior to a multiscale method for four *in vivo* examples with passive dorsiflexion.

This chapter has presented the components of the AutoQual block matching elastography algorithm: a new method that composes Quality Determined Search and 2D bicubic spline interpolation of the signal together with Automatic Search Range and Adaptive Block Size features to track image texture of RF ultrasound signals. This method has been applied specifically to the problem of assessing motion and strain in the image-lateral direction for superficial tissue, such as Achilles tendon and has quantitatively and qualitatively been shown to provide superior performance to a multiscale block matching algorithm. These assessments have taken the form of a simple, intuitive rigid motion and image-lateral compression of a gelatine phantom in a mechanical test machine to measure quantitative differences, and assessments of *in vivo* healthy and ruptured Achilles tendons for qualitative purposes.

The phantom block experiments successfully showed dynamic changes in the error from different speeds of rigid body motion, a steadily increasing NSE with increasing amounts of strain imparted and the change in standard deviation of the strain field with the speed of strain imparted. In all three of these phantom block tests the AutoQual algorithm equalled or outperformed the Multiscale method.

The *in vivo* examples re-emphasised the improvement of the AutoQual over the Multiscale algorithm, with a wider field of view for both displacement and (consequently) strain images, smoother displacement fields with fewer discontinuities, and higher normalised crossed correlation for recent ruptures, partially healed and healthy tendon examples.

Chapter 5

Optimisation of the AutoQual method parameters

5.1 Refinement of AutoQual Algorithm

The previous chapter describes work conducted in production of the publication of the article describing the AutoQual algorithm in the Journal of Biomechanics [172]. Subsequently, work has been conducted that uses the phantom data generated to further investigate and improve the performance of the algorithm by altering the user input parameters.

With the creation of the controlled test data from the phantom experiments, a useful tool has been gained that can allow the investigation of the effects of some of the parameters used in the tracking algorithm. By using the metrics of displacement accuracy, strain accuracy and strain field variation on idealised physical tests with a known ground truth, the dynamics of some of the attributes have been investigated and better settings have subsequently been established. The AutoQual algorithm was applied to samples of the phantom test data with different algorithm parameter settings in order to find the best possible parameters to find accurate strains which minimise variation in a controlled strain field yet retaining resolution.

5.2 Seed point placement

Initial experimentation was carried out to investigate the placement of the ‘seed’ points in the AutoQual algorithm. The method described by Chen et al. with seed points distributed throughout the image was tried on several *in vivo* examples with image-lateral tendon motion. Occasional analyses had large areas of displacements highly influenced by a few erroneous seed blocks. It was found that using the seed points at 10% from the top of the image and evenly spaced across the width gave a more repeatable and continuous result compared to calculations that included seeds from deeper in the image. It may

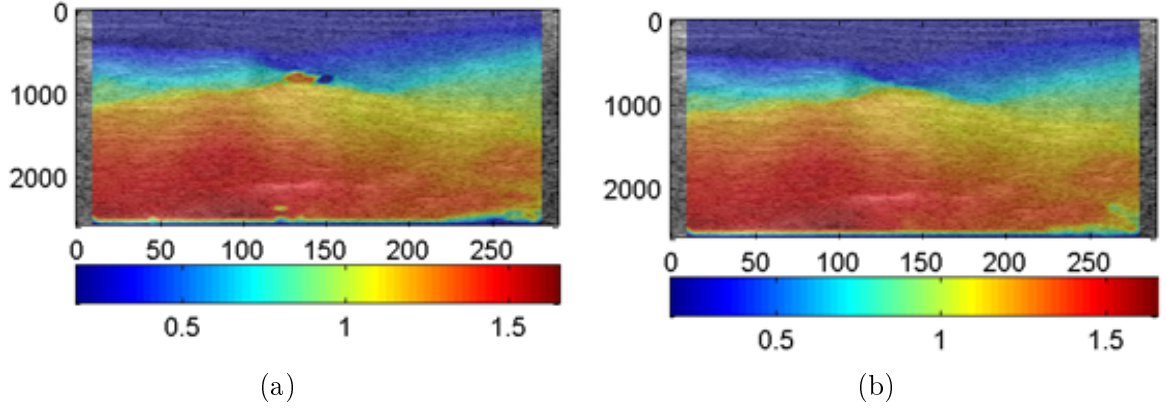


Figure 5.1: Examples of displacement fields obtained by the AutoQual algorithm (a) SSD cost (b) NCC Cost.

be that for fast motions with high amounts of shear between structures that this may need to be re-evaluated, but examples of this were not found in this dataset. Chen et al. do describe a method which performs a second pass over a calculated displacement field and recalculates any small regions, the premise being that they will always have lower correlation coefficients than the surrounding regions. Although this does work, we have found that for our data sets the applicable instances are relatively rare, and are insignificant in the case of lateral elastography where discontinuities tend to be due to shadows or out of plane motion and consequently can be relatively large and would not be removed by this method. Another potential influence is signal block size, as we have used much larger blocks than those reported by Chen et al. and this should reduce the effect of very small regions of decorrelation.

5.3 Cost function

In the initial AutoQual algorithm NCC, rather than SSD cost was chosen, principally as it scaled well with adaptive block sizes and appeared to give a smooth displacement field.

Several *in vivo* examples using both image-lateral and axial motions were assessed with both NCC and a normalised SSD (SSD/block size in pixels). As found by Chen et al. erroneous small areas of high displacement values were found with the SSD cost, but these are eliminated or greatly reduced in our implementation using NCC, particularly when using the RF domain signals rather than the signal envelope or phase alone.

5.4 Spline interpolation assumptions

There are many potential variations in how to computationally decide on the coefficients for the 2D bicubic spline algorithm. In the signal direction, a cubic spline which allows overshoots and has a continuous second derivative is intuitive - it is a common method for signal processing and provides realistic approximations of smooth, continuous signals. It was proposed that a cubic function that does not allow overshoots of the spline interpolation in the image-lateral direction would provide a more accurate interpolation. In this formulation, the initial set of x-axis cubic splines are generated with the Matlab function '*pchip*' while the z-axis splines are generated using '*spline*' as per the original experiment previously described. '*pchip*' generates splines similarly to the '*spline*' function but with the extra constraint that the first derivative of the spline coefficients on successive interpolation points must be of the same sign or equal to zero. Examination of sections of splines formed in this way show that the linear term of the cubic spline dominates in these cases.

The AutoQual algorithm recalculated the displacement fields for all of the previously mentioned displacement-only phantom test US sequences and a selection of compression tests and *in vivo* examples.

Results were inconclusive; steady-state speeds errors for the phantom displacement tests for the zero-overshoot (ZO) splines were shown to be greater than those found with the overshoot allowed (OA) splines, as shown in figure 5.2. However, strain fields of the phantom compression tests were found to be beneficial as strain fields from the ZO spline formulation were more uniform in appearance and had correspondingly lower standard deviations of strain across the field.

In practice, on *in vivo* examples, the different spline generations gave very similar results, although notably lower variation in strains was observed in deeper tissues from the ZO splines. Without a ground truth it is difficult to quantify which of these formulations is the superior for *in vivo* examples, there appearing to be a trade-off between absolute accuracy of tracking texture patches and in the uniformity of strain achieved. For future formulations it was decided that the more sporadic ZO spline formulation was less desirable and that the OA splines should continue to be used.

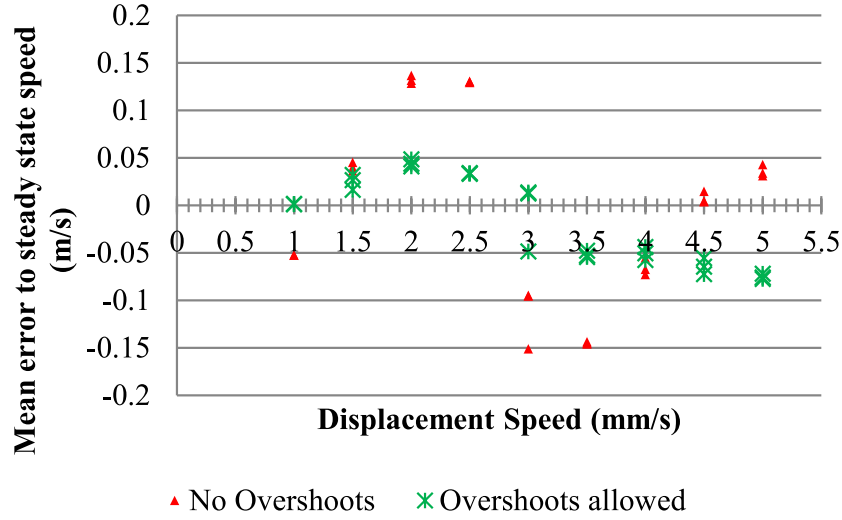


Figure 5.2: *The standard deviation of lateral elastography strain fields from induced strains on a phantom block at various grip-to-grip speeds for AutoQual and Multiscale methods.*

5.5 Strain window size

Both the AutoQual and Multiscale algorithms shared the function that generates the strain images in x and z directions from the summed total displacement image. In this, as stated in section 4.4.3.4, linear fits of displacement are made in both directions using lines from the 2D window as multiple series of the fit and weighted by the NCC at each point. For a homogeneous material experiencing uniform compression, the length of the sample window would not make a difference to the average strain calculated. This was found to be exactly the case for the phantom block experiment: there was zero change in average calculated strain for window widths of 1-8mm. Predictably, there was a decrease in standard deviation of the strain field for larger window size as small perturbations in the displacement fields were averaged out over longer distances as shown in figure 5.3 and figure 5.4. The compromise on real images will be based on the minimum feature size and the acceptability of blurring boundaries between tissues of different stiffnesses. In the application of Achilles tendons post rupture, it should be restated that the primary concern is not detection but quantification, that boundaries between tissue types are themselves indistinct (especially if the rupture is recent) and that those boundaries only appreciably exist going across the z -direction. As healthy Achilles tendons are only up to 5mm thick, a strain window depth of more than 1mm would be inappropriate for imaging

purposes, but strain window widths of more than this could be acceptable. However, extra consideration should be taken about areas of poor correlation where discontinuities in the displacement field exist. Here, large window size could lead to those small discontinuities appearing as large areas of erroneous strain and therefore affect regions of interest, even where there is good correlation and a smoother local gradient of the displacement field.

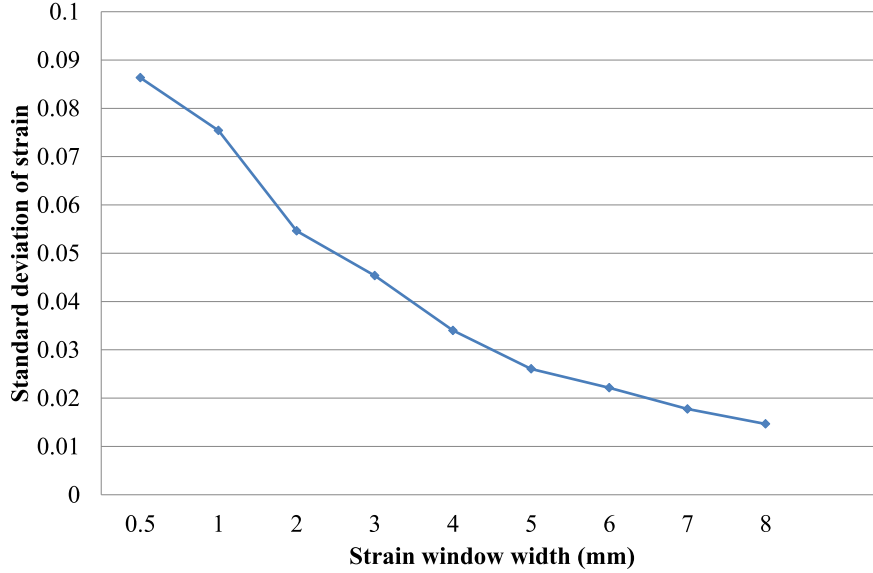


Figure 5.3: *The standard deviation of lateral elastography strain fields from induced strains on a phantom block 2mm/s grip-to-grip speed for various strain window widths*

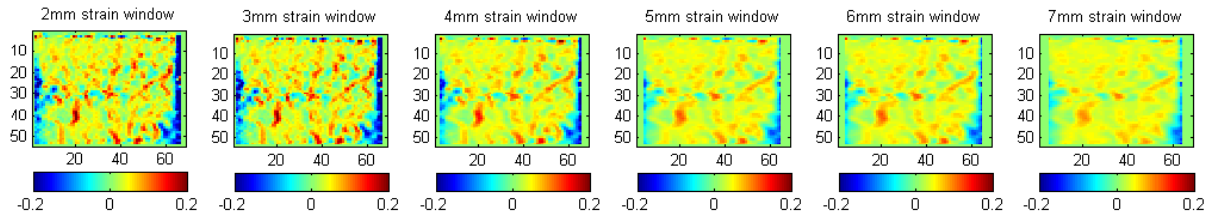


Figure 5.4: *Elastography strain field images from induced strains on a phantom block 2mm/s grip-to-grip speed for various strain window widths*

5.6 Automatic search range (ASR)

In the phantom block experiments, a uniform strain was imparted on a homogeneous block at a constant speed and so it can be expected that adjacent matching blocks of image texture should have similar displacement values to those of its neighbours - this is the implicit assumption used for the ASR. Results showed zero difference in changing the

automatic search range to allow either a very tight search (± 1 pixel in the x -direction) or for a wide range (± 8 pixels) for grip-to-grip compression speeds of 2mm/s or 5mm/s.

Additional tests on *in vivo* examples also showed zero difference from allowing greater search ranges for one healthy example and a very small change in the strain estimated for a fast moving recent rupture case. For this recent rupture case, the mean difference in point values of displacements was 0.078mm and differences in the strain or displacement images were minor and not qualitatively different. While it cannot be guaranteed that this will be the case for all examples, it appears that the AutoQual algorithm is extremely insensitive to changes in the lateral automatic search range. The conclusion from this is that the act of centering the search range and initial displacement estimate has a greater impact for lateral motion than additional restriction of the search range.

The lack of effect of changing the automatic search range can partly be attributed to the Adaptive Block size feature. Where there is good continuity of motion and relatively low strain the Adaptive Block Size feature would rarely need to be employed except in local regions of high displacement, image edges or where the search region has been specified to be small. It can also be beneficial in cases where signal decorrelation can cause a bad initial estimate. In this case, the ABS prevents the erroneous displacement estimate propagating by allowing better solutions to be found once the area of poor correlation has been left, while still somewhat restricting the search range to a value similar to those found close by. The benefits at the image edges appear consistent in analyses, improving the accuracy in these regions and increasing the field of view of strain and displacement imaging, particularly where large block sizes are used.

5.7 Block size

The block size used for the matching algorithm is significant; small blocks have the potential to more accurately track areas of tissue that may move independently of surrounding tissue which is important if the test image contains an amalgam of different tissues. Small block sizes reduce the impact of issues arising from tissue boundaries, where tissue shear may distort the tissue appearance or motion from one tissue may influence the tracked motion of the boundary in a disproportionate manner.

Block widths of 4 to 32 pixels were used to track the same phantom block compression image sequence of a 2mm/s grip to grip speed and a 4.6% strain imparted. This test was used for all parameter optimisation experiments unless otherwise stated. Figure 5.5 shows a contradictory message - that the standard deviation of the strain field decreased with larger block sizes but that the error in the strain measured became greater. This is believed to be due to larger window sizes causing tracking to be conservative by being influenced by the majority of the tissue in the block which moves a small amount and not by that which moves the most. Maximum displacements tracked were slightly higher for smaller blocks than larger ones (up to 0.079mm higher for a window width of 12 pixels compared to one of 32 pixels) while the minimum displacement were more similar at all block sizes.

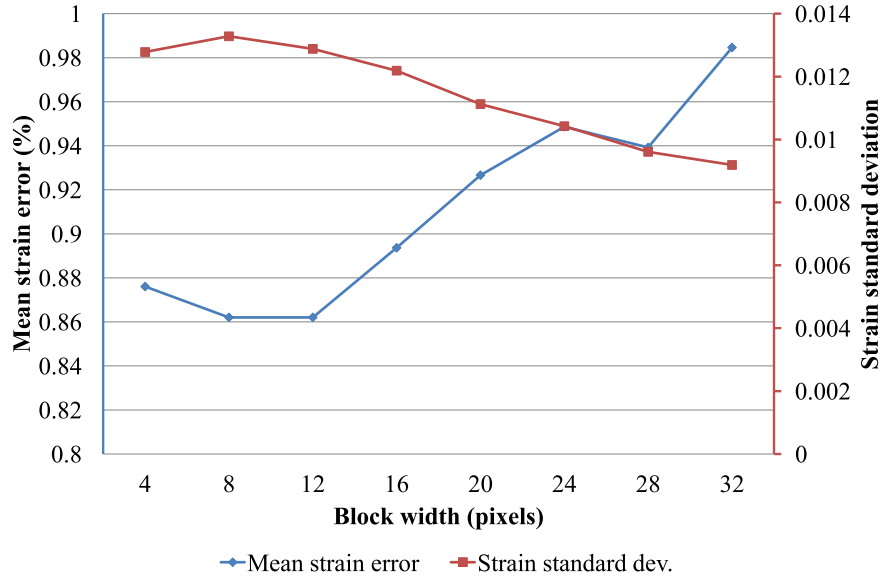


Figure 5.5: Mean strain error and standard deviation of strain fields found from block matching with various block widths from phantom compression experiment with grip-to-grip speeds of 2mm/s.

Block height also had an effect on the variation in the strain field, the average NCC and (surprisingly) the average strain error. Average strains were underestimated more with larger window sizes, as with window width. It is less clear why a larger block size in the vertical direction should inhibit tracking in the horizontal, but it is hypothesised that as the phantom block distorts in both directions and larger blocks will include more of the signal length then correlation will decrease. This flattens the dynamics of the cost

function, making the maximum NCC point less distinct and less sensitive for each block to changes in small regions.

It is concluded that a block width of 12 pixels and a height of 30 pixels produced the most beneficial results, minimising the strain error while providing some benefit of reducing strain field standard deviation. It should be noted that this value is likely to only be valid for US probes with the same piezo-electric element number, size, and spacing to that used and similar experiments would need to be carried out to assess optimum parameters for other probes.

5.8 Sparseness interval

The ‘sparseness interval’ describes how many blocks will be matched over the image. A dense interval will provide a greater resolution of image, but will be computationally more intensive and may increase noise, especially as it will decrease the effectiveness of median filter regularisation to smooth over areas of poor correlation. In addition, the use of the Quality Determined Search could be affected by the interval: too great a distance and the assumption of displacement continuity could become invalid; too small an interval could lead erroneous blocks to influence more neighbours than would otherwise be the case in areas of low signal.

The AutoQual algorithm analysed a compression example as in section 5.7, with various intervals between blocks. Interval spacing was found to have a stronger effect in the x-direction than in the z-direction for this experiment. Z-interval had almost zero effect upon strain field standard deviation, and lower intervals yielded a very slight increase in mean strain error of approximately 0.1% lower error for an interval of 30 pixels (approximately 1.2mm) than for intervals of 10 pixels (approximately 0.4mm). Changes to the x-direction interval gave almost twice the standard deviation in strain field at intervals of 1 pixel (0.2mm) compared with an interval of 3 pixels (0.6mm) which was found to be optimal for this parameter. However, it also gave the largest strain error, over 0.25% strain more error for 3 pixel interval compared to 1 pixel, and 0.21% strain higher than an interval of 4 pixels.

The selection of this parameter is more of a design decision and a trade-off than an

optimisation. An interval of 1 x 10 pixels provides the highest resolution tested and the lowest strain error for this experiment, while an interval of 4 x 30 pixels provides a reasonable compromise of smoother strain field and low error, but sacrifices final resolution.

5.9 Summary of parameter optimisation

This chapter has attempted to define the optimal parameters for the AutoQual algorithm based upon its use with a phantom block as ground truth. The exercise has provided insights into the performance of the algorithm with respect to those different parameters: spline interpolation restrictions, strain window size, automatic search range quantities, matching block sizes and sparseness interval. The findings are summarised in table 5.1. One of the gratifying findings of this optimisation exercise has been to find that changes to the strain window size and search range parameter have close to zero effect on the output. Block size, while being found to affect the output, did not have a destructive effect on the end result. The AutoQual algorithm has, therefore, been found to be robust to user input.

Changes to the interval between block centres did affect the results, as the QDS part of the algorithm allows the results of blocks to affect their neighbours. Likewise the block size was found to affect results, with larger block sizes causing an underestimation in material strain, but a smoother strain field and lower noise.

Optimum parameters based on this experience have been selected, allowing the AutoQual algorithm to be used with confidence that the results will have a good performance for a range of conditions that can be expected for *in vivo* image-lateral elastography of ruptured Achilles tendons.

This chapter has presented the components of the AutoQual block matching elastography algorithm: a new method that composes Quality Determined Search and 2D bicubic spline interpolation of the signal together with Automatic Search Range and Adaptive Block Size features to track image texture of RF ultrasound signals. This method has been applied specifically to the problem of assessing motion and strain in the image-lateral direction for superficial tissue, such as Achilles tendon and has quantitatively and qualitatively been shown to provide superior performance to a Multiscale block matching

Parameter	Comment	Chosen setting	Difference from previous setting in chapter 4?
Zero Overshoot Splines	Improved strain field smoothness, decreased accuracy at some speeds.	Overshoots allowed	Same
Strain window size	No effect on strain error for homogeneous phantom. Consideration of tissue sizes should be taken into account.	2mm x 2mm window	Changed
Automatic search range	Zero effect on homogeneous phantom. Small effect <i>in vivo</i>	2 x 5 pixel ASR	Changed
Block size	Larger block sizes cause underestimation of strain but decrease noise. This effect is stronger for image width	12 x 30 pixels	Changed
Sparseness	Higher intervals lowers the resolution of the strain field. Higher interval makes the strain field smoother but affects local accuracy and impacts the QDS effect	4 x 30 pixel between window centres.	Changed

Table 5.1: *Key parameters in the AutoQual algorithm and their effect upon the results.*

algorithm. These assessments have taken the form of a simple, intuitive rigid motion and image-lateral compression of a gelatine phantom in a mechanical test machine to measure quantitative differences, and assessments of *in vivo* healthy and ruptured Achilles tendons for qualitative purposes.

Chapter 6

Longitudinal study of changes in Achilles Tendon Post Rupture

6.1 Background

This chapter describes a pilot elastography longitudinal analysis of a clinical study of 21 Achilles tendon rupture patients over 24 weeks of healing. Ultrasound image sequences of the affected Achilles tendons were acquired that capture tissue deformation produced by two different methods - manual probe compression and ankle flexion. The AutoQual quantitative elastography algorithm (as described in chapter 4) was applied to the sequences to find the strain imparted. The strain and spatial measurements from ultrasound were analysed in conjunction with existing clinical measures of healing in the Achilles tendon over the healing period.

6.2 Motivation

Currently, there is no universal gold standard for assessment of healing or of health for Achilles tendons. Potential uses for any metric could be:

- to assess the efficacy of alternative treatments or differences in populations (due to age or exercise) between groups of subjects.
- to assess the response of an individual to treatment over time to assess progress.
- to be used as diagnosis for chronic conditions.
- diagnosis and prediction of pathology so that preventative action can be taken.

Many groups have developed their own clinical metrics for assessment of Achilles tendons in their studies based on measures of motion, maximum force and perceived pain response, yet the majority have little or no published validation studies [39].

Two preferred versions of these types of metrics which have been somewhat validated are the Achilles tendon rupture score (ATRS) [40] and the Victorian Institute of Sport

Assessment-Achilles questionnaire (VISA-A) [44]. These assess patients with a scoring system with combinations of direct measurements of movement or strength capabilities as well as patient scoring of pain responses. There are potential problems with these methods: a potential lack of responsiveness to changes in underlying conditions (as some conditions could have reduced symptoms), a lack of specificity (as patients may have disproportionate pain perception or baseline capabilities), and may not be predictive of future risk.

While there is no guarantee that assessment of mechanical properties will be predictive, there is a growing body of literature supporting the view that mechanical properties (principally stiffness and Young’s modulus) to describe functionality [57–59] and measures of these could offer a more objective measure of tendon performance. Significantly, Schepull et al. concluded that strain and stiffness measured by Roentgen stereophotogrammetric analysis (RSA - high precision stereo X-rays) correlated well with a clinical outcome measure (their own ‘heel rise index’ and the Therman score [183]) and may be predictive of the final outcome [111].

The RSA method has provided some beneficial insights into the healing process of tendons as a research tool [31, 112], yet it has a number of significant limitations: (i) it involves surgically implanting tantalum beads; (ii) there is limited proof that the beads maintain tissue position under stress without migration; (iii) only overall average strains for the tendon between bead implants are found; (iv) imaging requires X-ray exposure of the subject to a radiation dose; (v) the applied load is static not dynamic, making it difficult for further study into the viscoelastic properties of the tendon.

Ultrasound elastography has the potential to solve some of these issues and provide a quantitative measure of tissue mechanical properties that can be used for both research and clinical practice. Images can be targeted at the rupture site, enabling analysis of the tissue that experiences the greatest change in composition throughout the healing process and therefore being as responsive to changes as possible. No implantation is required and ultrasound imaging is a safe and cost/space effective technology. It has a fast frame rate, making it capable of capturing dynamic motion which can be used for both investigation into elastic and viscoelastic behaviours.

Elastography has previously been explained in detail in this thesis (see 3.6.1 and chapter 4).

Existing analyses of the clinical benefits of ultrasound elastography for assessing tendons have concentrated on the appearance of the palpation elastography implemented in many current commercial systems [152, 153, 184]. Previous studies of the use of elastography in the image-lateral direction are limited, and are mainly concerned with the development of algorithms based strains imparted in healthy *ex vivo* tendons [139, 171] and do not account for the difficulties in performing lateral elastography analysis on *in vivo* cases or those with ruptured or damaged tendons. Post-rupture subjects present particular problems as the image texture is significantly disrupted at the rupture site, with signal attenuation, shadows, a mixture of image textures, as well as patient considerations for pain and acceptable force/motion range that can be imparted.

6.3 Longitudinal study overview

This clinical study was conducted with two motivations: a clinical assessment of the differences between two rupture patient groups treated with platelet rich plasma (PRP) and a control group, and the assessment of the use of elastography derived metrics to assess healing in Achilles tendons. The focus in this chapter is the analysis of elastography and the results relating to the clinical aspects are not the focus of discussion.

Ultrasound RF motion sequences were acquired for each patient at intervals along their healing progress by the clinician administering the PRP aspect of the study. Motion sequences were captured with palpation motion by manual compression/decompression of the US probe against the subject's skin in the affected area and from performing passive motion of the tendon by non-voluntary flexion of the subjects foot and ankle ('ankle flexion').

Apparatus for smooth, repeatable longitudinal stretching of the Achilles tendon by ankle flexion is described and data analysed to show the reproducibility of results compared to manual palpation are presented. The resultant 2D strain fields are described for both manual palpation and ankle flexion motions to improve awareness of the limitations of the imaging technique.

The use of cross-sectional area of the Achilles tendon is investigated to corroborate findings from other studies as to its applicability to use for tissue modulus calculation. Mean strains at the rupture site are analysed as to their correlation to changes across time and compared to the VISA-A and ATRS clinical values and the responsiveness of the changes seen in patient groups as time progresses is discussed.

The chapter concludes that these are promising initial results and that further efforts can focus on improving accuracy and decrease variability, thereby increasing the selectivity of results.

6.4 Patient groups

The study includes 21 subjects who had all suffered a complete rupture of the Achilles. Human data acquisition was approved by the Oxfordshire Ethics Committee B (reference 09/H0605/78) and registered at the International Standard Randomized Controlled Trial (ISRCTN93608625). It conformed with the current revision of the Declaration of Helsinki and ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

Patients were male and female participants aged between 18-55 years and were presented within 72 hours of rupturing the Achilles tendon. Patients had no previous history of Achilles tendon injury, diabetes, haematological or renal disorders, no evidence of gangrene, ulcers or vascular disease, no history of alcohol or drug abuse, were not pregnant and are otherwise considered to have been healthy.

The patients were being treated in two different ways, by injection of PRP to the rupture zone and a control group who received a saline injection at the same site. Patients were blinded as to which group they were in. PRP is a proposed treatment for trauma in which a high concentration of the subject's blood-platelets is injected at the rupture site and provides biochemical signalling and material that may promote the healing response [185]. In addition, some patients from each treatment group were surgically treated with suture to hold the ruptured tendon ends together, while others were treated conservatively with no surgical intervention. These treatment groups are shown in table 6.1. The decision to take surgical intervention is based on ultrasound assessment of the gap size between the ruptured tendon ends [32] and was not a designed parameter for investigation in

this study. The average rupture location was 4.8cm from the tendon insertion at the calcaneum. 19 of the subjects suffered Achilles tendon rupture due to injury from sports, one from walking up stairs and one jumping from a short height at work. One patient suffered a re-rupture over the course of the monitored period. Subjects all undertook the same treatment and advice. Surgically and conservatively treated groups had slightly different immobilisation regimes according to the Sheffield regime protocol for Achilles tendon rupture (Table 6.2) [186].

Patient Group	Surgical Treatment	PRP injected	Number of patients
S+PRP	Yes	Yes	6
S-PRP	Yes	No	4
C+PRP	No	Yes	5
C-PRP	No	No	6

Table 6.1: *Description of different treatments received by patients for this study.*

Restriction	Physiotherapy	Operative treatment	Non-operative treatment
Solid Cast	None	week 0-1	week 0-6
Removable Cast	Increase motion	1-4 weeks	week 6-12
No Cast, Optional crutches	Increase motion & strength	week 12-18	week 4-18
Return to running allowed	-	week 18+	week 18+

Table 6.2: *Cast types used by patients during rehabilitation.*

Patients were recruited by a clinical fellow (Dr. Joseph Alsousou) who also performed the ultrasound scans and collected the VISA-A and ATRS results. All other analysis presented here was conducted by this thesis' author unless otherwise stated who was not blinded to the different treatment groups although analysis was conducted in an automated fashion where possible.

The primary assessment of healing was based on clinical measures, such as pain response and patient mobility (primarily the VISA-A [44] and ATRS [40] questionnaires) and histological examination of biopsy samples of the damaged tendon taken 3 weeks and 6 weeks after the initial rupture (not reported here).

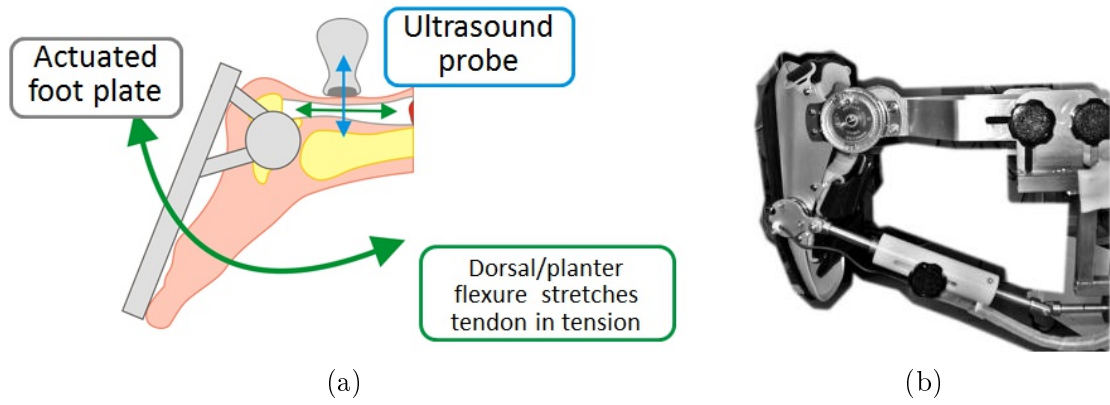


Figure 6.1: (a) Summary of the movements used to mechanically stimulate the tendon during ultrasound sequence acquisition. (b) The computer controlled motorised foot cuff used to perform controlled flexion of the subject's ankle and foot.

6.5 Measurements taken

For each subject ultrasound RF signal sequences were acquired at the rupture zone in the sagittal plane, along the tendon from the posterior of the leg looking toward the leg bone. The ultrasound system was a Zonare z.one (ZONARE Medical Systems, Inc, Mountain View, CA) with a L14-5 linear transducer, central frequency 12MHz, frame rate 13.4Hz. Sequences were acquired with two different forcing conditions: a release from compression of the tissue with the ultrasound probe in the probe-axial direction ("manual decompression") and a tensioning of the Achilles tendon by passive flexion of the ankle with both 'toe lifting' dorsiflexion (DF) and 'toe pointing' plantar flexion (PF). These motions are summarised in figure 6.1(a). These ankle flexion motions were achieved in a controlled manner with repeatable speeds and range of motion by the use of a custom made robotically controlled foot cuff (figure 6.1(b)). This foot cuff receives user input from a custom Matlab GUI which initiates a stepper motor at a set speed which then articulates the foot cuff and induces ankle flexion. The foot cuff also contains a 3-axis force transducer and electromagnetic mechanical linkage which can be broken if the force exceeds a pre-set limit or if the subject presses a button. This is to ensure patient safety when manipulating their damaged limbs. However, the range of motion and anticipated forces should be very small and significantly less than those experienced in weight bearing during walking.

Ultrasound RF signal sequences that were captured during motion typically had a

duration of approximately 3 seconds and were acquired at an ultrasound central frequency of 12MHz and frame rate of 13.4Hz. Signal data from the Zonare machine is initially stored in IQ format (demodulated) from which the RF signal can be reconstructed. Manual decompression sequences were typically of approximately 16 frames duration and DF/PF sequences were of 38 frames consistently. Frame selection was performed manually to select sequences where the motion is in a consistent direction using a custom Matlab software GUI. All sequences were captured by an experienced clinician who ensured that the image plane was in-line with the direction of the subject's tendon and that probe slippage was minimum.

These ultrasound RF sequences were then analysed with the AutoQual algorithm to establish the estimated displacement and strain fields. In addition to the image-lateral and axial strains previously described, the principal strain-field was also derived. Principal strain is based upon an element-wise analysis that describes the maximum strain at the point by taking into account the axial, lateral and shear strains found. Principal strain is found by rotating the arbitrary x and z axes for each location in order to minimise the apparent shear strain and maximise the orthogonal strains found. This is found in a computationally efficient manner as given by equation 6.1.

$$\varepsilon_{1,2} = \frac{\varepsilon_x + \varepsilon_z}{2} \pm \sqrt{\frac{\varepsilon_x - \varepsilon_z}{2}^2 + \varepsilon_{xz}^2} \quad (6.1)$$

where $\varepsilon_{1,2}$ are the two orthogonal principal strain values, ε_x and ε_z are the linear strains in the x and z directions and ε_{xz} is the shear strain given by:

$$\varepsilon_{xz} = \frac{1}{2} \left(\frac{\partial u}{\partial z} + \frac{\partial w}{\partial x} \right) \quad (6.2)$$

where u and w are the x and z displacement vector components respectively.

For this version of principal strain imaging, the maximum principal strain is used.

Elastography measurements were targeted at the site of the rupture and were acquired at 0, 1, 3, 6, 8, 12 and 24 weeks since the rupture occurred. One or two repeat acquisitions were made at each time point. There are some instances of missing data due to patients missing appointments or a technical failure in the data acquisition process. Notably,

patients 1-5 are missing some data using the controlled motion device due to a lack of availability at the time.

For all manual-axial, PF and DF motions, the resultant B-mode, strain and displacement images were individually assessed by a trained clinician and poor quality images were rejected. The region of interest (ROI) at the tendon rupture zone was manually segmented in the first frame of the sequence using all the available images: the ultrasound B-mode image, the displacement fields and strain fields. This assisted the confidence of selecting the tendon region accurately, which can be difficult to assess in rupture cases.

The ROI were selected to avoid obvious artefacts- where large artefacts were present at the rupture zone, ROI were selected of nearby tendon in the same image. Reported strains for each subject are the mean values of the relevant strain fields over the selected zone. The standard deviation of the strain field was also captured for reference.

Segmentation, image review and database information for each record were accessed by another custom Matlab GUI which allowed easy access to view the results for each individual record. Input of database information via this GUI (patient number, week number, unique analysis number, motion type, tendon section, patient group, flags for if the healthy or ruptured tendon was measured or if the record should not be included- see figure 6.2) facilitated a fast summarising of the data for statistical analysis while maintaining the value of individual record review.

Transverse plane ultrasound sequences were also acquired in order to measure tendon cross-sectional area at the rupture site. Cross-sectional area is measured here with two methods: by placing two chords across the transverse plane image and assuming an ellipsoid shape or by placement of three chords across the sagittal plane image and assuming a circular cross-section with radius equal to the mean of the three chords (figure 6.3).

6.5.1 Data metrics and analysis

Once data were acquired and block matching performed analysis was performed on the resultant trends and responsiveness from either *direct* metrics or from *derived* metrics, where the previously found direct metrics are mathematically manipulated or combined to form new quantities. Combining these metrics may gain more meaningful insight into the

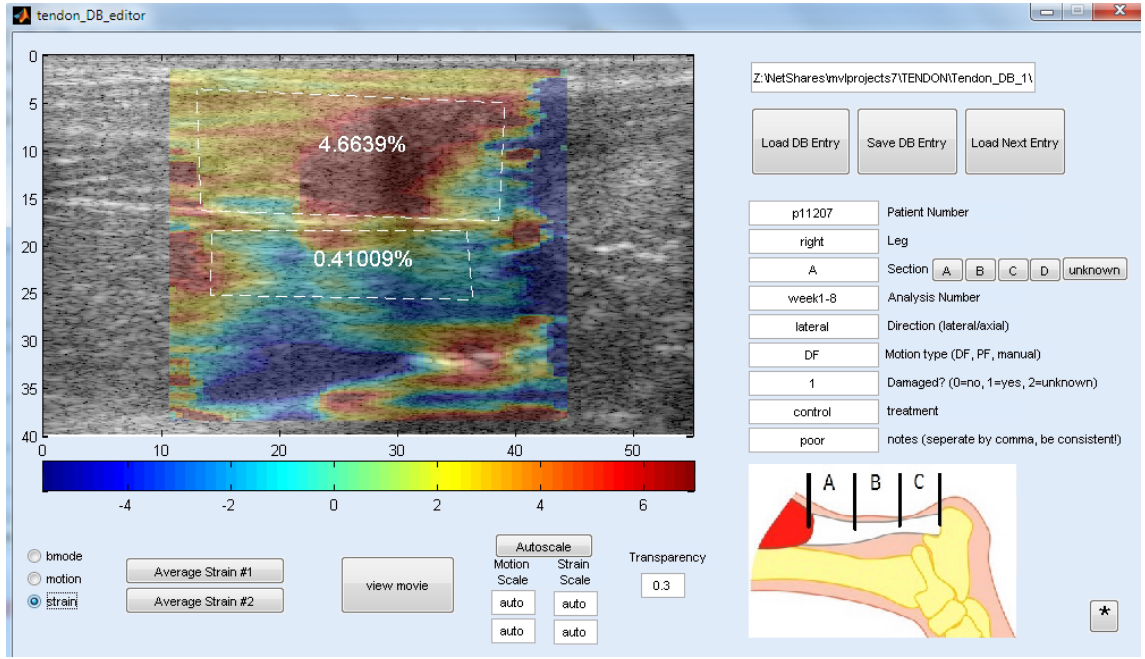


Figure 6.2: A view of the Matlab GUI developed to allow review and data storage of patient tendon data.

changes in mechanical properties and thus may minimise some of the variation between patients or accentuate differences between patient groups.

The *direct* data metrics acquired for each sequence are: the mean lateral strain (ε_x - DF/PF motion only) or axial direction (ε_z - manual decompression motion only) at the rupture site; the mean maximum principal strain (ε_p) for all motion types; and the tendon cross-sectional area (CSA - measured by two methods).

The *derived* metrics of interest are: reciprocal of lateral/axial/principal strain ($1/\varepsilon_x$ - DF & PF motions; $1/\varepsilon_z$ manual axial motion; $1/\varepsilon_p$ all motions), reciprocal of strain

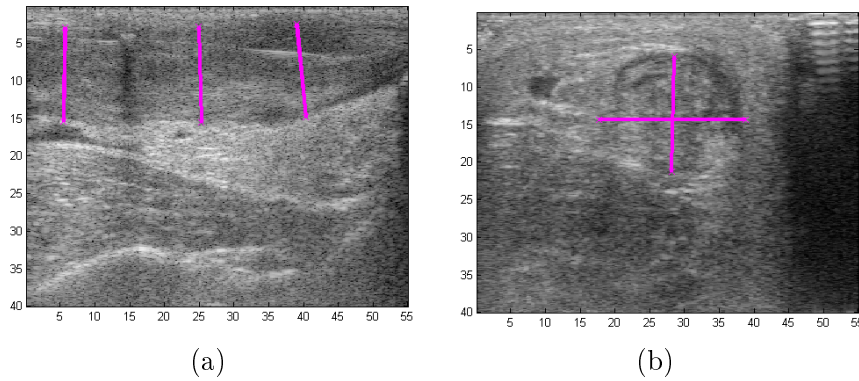


Figure 6.3: (a) Example of 3 manually placed chords taken from a sagittal plane B-mode image to calculate CSA . (b) Example of 2 chords taken from a transverse plane B-mode image to calculate CSA .

times CSA for lateral motions ($1/\varepsilon_{x,p.CSA}$) and strain divided by CSA for lateral motions ($\varepsilon_{x,p}/CSA$).

The justification for these derived metrics follows: the underlying material property that is assumed to be of interest is the tendon's elastic Young's modulus (equation 6.3, where E is the Young's modulus, σ is the stress imposed and ε is the resultant strain). If a constant force is considered to have been applied then the material modulus can be considered proportional to the reciprocal of the products of the strain and the cross-sectional area, A (equation 6.4).

$$E = \frac{\sigma}{\varepsilon} \quad (6.3)$$

$$E \propto \frac{1}{A\varepsilon} \quad (6.4)$$

By using this value the intention is to more truly capture the changes in material properties which are influenced by morphological changes to tissues to make them more robust to tensional stress while they are vulnerable. However, there is a risk that the compounded measurement error could lead to a more noisy metric, so the simplest case of assuming a constant cross-sectional area (therefore constant stress) is also considered (equation 6.5). This is also has an aesthetic value in that the values should increase over time, so that healthy tendons have a high score and damaged have a low score.

$$E \propto \frac{1}{\varepsilon} \quad (6.5)$$

However, it has been noted in previous works that the cross-sectional area of the Achilles tendon is expected to increase in the first 24 weeks of treatment [111] and that the strain for a given force is also expected to decrease as the tissue becomes stiffer- it may therefore be expected that multiplying these figures will have a nullifying effect and make the resultant metric less dynamic to changes over time. A more complementary way of combining strain and cross-sectional area may be to divide one by the other. A mechanical justification for this is that the resultant metric would be proportional to the amount of energy per unit volume imparted to the tissue during tension for a repeatable applied force. For a linearly elastic material the energy per unit volume is described by

equation 6.6.

$$\frac{U_e}{AL} = \frac{1}{2}E\varepsilon^2 = \frac{1}{2}\sigma\varepsilon \quad (6.6)$$

where U_e is the tensile energy. If a constant applied force is assumed, then the energy will be proportional to the strain measured divided by the cross-sectional area.

For a repeatable force this becomes:

$$\frac{U_e}{AL} \propto \frac{1}{2} \frac{\varepsilon}{CSA} \quad (6.7)$$

6.5.2 Metric viability tests

These direct and derived metrics need to be tested to establish the responsiveness of the measure to changes between check ups, the conformity to a supposed trend, the correlation/similarity of conclusions to the existing clinical measures and the repeatability of the measures to establish if the methods are error prone. Additionally, it is of interest to see if there is a discernible difference between the PRP treated and control groups as well as between the surgically treated groups and the conservatively treated groups (it is deemed that there is too little data to treat these as four completely separate groups).

Results are presented both with all data points included and with outlier removal by a version of Chauvenet's criterion for each week. Here, points more than 1.5 standard deviations from the mean value are excluded. The tests are as follows:

Image signal to noise ratio (SRN_i : equation 6.8) of the strain field is measured in order to compare the responsiveness of the strain measures to the selection of the affected area and can be compared between principal and lateral strains (for DF/PF motion) or axial strains (for manual decompression) as well as observing how this responsiveness changes over the progression of healing. A good measure should have a high signal to noise ratio, indicating that the variation in strain values within the selected area are small compared to the mean value of the strain.

$$SNR_i = \frac{\mu_\varepsilon}{S_\varepsilon} \quad (6.8)$$

where, μ_ε is the mean value of strain field within the selected tendon region, S_ε is the

standard deviation of the strain field within the selected region.

Repeatability of each parameter was tested with the average coefficient of variation (CoV) (equation 6.9) for each experiment. This provides a test for repeatability that compensates to the fact that the different metrics (e.g. strain, cross-section area) have greatly different quantities - CSA may be in the order of 100mm², whereas strains may be in the order of 1-10% and so are not directly comparable. This could also be thought of as a signal to noise ratio, but this term is avoided to avoid confusion with image-SNR. These tests are, by necessity, performed for repeat experiments for the same patient, time since rupture and motion type, the variation across the patient groups is accounted for in the correlation tests.

$$\overline{CoV} = \frac{\sum_{n=1}^N \frac{S_n}{\mu_n}}{N} \quad (6.9)$$

where n is the individual experiment number (one for each patient, week and motion type combination), N is the total number of measurements used, μ_n is the mean value found for the repeated experiment n , S_n is the standard deviation for experiment n .

In addition, to compare repeatability between the different motion types, a simple standard deviation of all measures directly taken is presented. Each result was redatumed by the mean value of the repeated experiment (equation 6.10) and the standard deviation of all results was then found - this allowed the use of much greater group sizes than used for the CoV calculation and so should provide a more accurate repeatability measure, but will not account for inherent differences in the quantities presented:

$$A'_{i,j} = A_{i,j} - \overline{A_i} \quad (6.10)$$

where A' is the resultant value from which the standard deviation across all experiments was compared, A is the metric being tested for experiment j (same patient, week and motion type), repeat number i , and $\overline{A_i}$ is the mean value of the metric for that experiment.

Correlation was measured using Spearman's rank correlation that appropriately tests for a monotonic non-linear relationship. Results from output metrics were tested against

the time since rupture and against the VISA-A and ATRS clinical metrics.

Responsiveness was measured by performing the student t-test between the results of each week with each other week. If the groups are distinctly different then the null hypothesis should be rejected, providing a lower P-value. The mean P-value for each potential metric is presented for each result. This test is considered as a level of confidence of the ability to identify the week at which any single data point fits. This is a more strict test than ANOVA, (although it should be noted that this has been conducted without Bonferroni correction). Balanced one-way ANOVA testing over the 7 week groups is also conducted for completeness.

Patient group discrimination is tested as it is of importance for clinical investigations to determine whether a difference between the alternative treatment groups can be measured. Dividing the subjects into four different groups as described in table 6.1 will provide groups that are too small to show any significance, and so two separate comparisons are made: between PRP and the control group and between surgically treated and non-surgically treated. For each week Welch's t-test is applied between the results for the two groups for each metric (equation 6.11), where the test statistic 't' is tested against the t-distribution with degrees of freedom v (equations 6.12). This tests the hypothesis that the two groups are independent sub-samples of the same distribution with equal mean values and unknown but equal variances and provides a probability 'P'.

$$t = \frac{\overline{X_1} - \overline{X_2}}{\sqrt{\frac{s_x^2}{N_1} + \frac{s_y^2}{N_2}}} \quad (6.11)$$

where t is the test statistic, X_i is the sample mean, s_i is the sample variance and N_i is the sample size.

$$v \approx \frac{(\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2})^2}{\frac{s_1^4}{N_1^2 v_1} + \frac{s_2^4}{N_2^2 v_2}} \quad (6.12)$$

where $v_i = N_i - 1$ is the degrees of freedom associated with the i^{th} iteration.

Groups are considered distinct from each other if the null-hypothesis is rejected and the probability of the test statistic against the probability density function of the t-distribution

(equation 6.13) with variance v is $P < 0.05$.

$$P = \frac{\Gamma(\frac{v+1}{2})}{\sqrt{v\pi} \cdot \Gamma(\frac{v}{2})} \left(1 + \frac{t^2}{v}\right)^{-\frac{v+1}{2}} \quad (6.13)$$

6.6 Results

6.6.1 Results collected

All patients completed the treatment, and the acquisition process caused minimal discomfort. One patient re-ruptured their tendon between week 8 and 12 (patient 6, see appendix figure A.1 for B-mode images) and some patients missed occasional appointments. Of the possible 147 data points for each motion type (21 patients, 7 time points), 120 points for dorsiflexion and plantar flexion were acquired and 132 points for manual decompression.

6.6.2 Results: B-mode and strain images of individual patients

B-mode images showed a degree of qualitative difference over the course of healing (a full example of this is shown in appendix image A.2, and a summary selection of images in figure 6.4). Generally, weeks 0-1 had a blood clot region clearly visible as a dark patch of the image. In these weeks the rupture zone visibly showed more deformation than surrounding material and the tendon end closest to the calcaneus moved more than the dorsal end with dorsiflexion passive motion of the foot and ankle.

Axial strain images of manual decompression clearly highlighted the rupture zone in weeks 0-1 and a visible change was usually present in weeks 0-3 (see example in appendix figure A.4). Deeper tissue usually experienced lower values of strain than ruptured tendon. Axial motion images with manual decompression (example in appendix figure A.3) were generally smooth and continuous with few discontinuities. Principal strain images (example in figure A.5) for manual decompression looked similar to axial strain images and had similar values in the region of the tendon but had higher and more noisy values in deeper tissue.

In weeks 3-8 the rupture zone became less distinct, and while there was often still a darker region in B-mode images it did not contrast to the surrounding tissue as much and did not cause visible shadows as often. Tendon boundary and tendon tissue contrast to

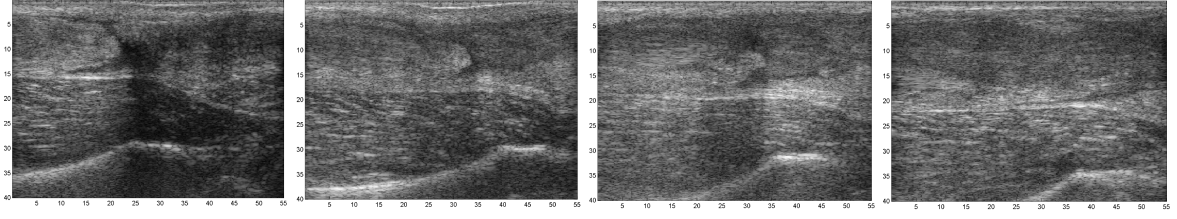


Figure 6.4: *Example of sagittal plane B-mode images of Achilles tendon rupture at 0, 3, 8 and 24 weeks post rupture.*

surroundings became lower in this period and in many patients a more acoustic-reflective callus region was apparent, usually to the dorsal end of the rupture site. Between weeks 8 and 24 this callus (if present) lessens in contrast to the remaining tendon. All tendon tissue becomes darker compared to surrounding tissue and the tendon noticeably becomes thicker in both the sagittal and transverse planes. In weeks 6-24, strain fields (both lateral and principal strains) were more uniform within the tendon region and there is little observable in each patient over the remainder of the observed period. Slip motion between tendon and surrounding tissue can cause apparent high strains, particularly visible in the principal strain images. During selection of ROI these regions were avoided where possible.

6.6.3 Results: Summaries of metrics' change over time

Summary boxplots of all of the metrics are shown for DF motion (figure 6.5), for PF motion (figure 6.6), for manual decompression (figure 6.7) and the changes in CSA measured in sagittal and transverse planes (figure 6.8). All parameters showed noticeable changes over the period covered.

Strain and reciprocal of strain measures all showed greatest change in weeks 1-8 (figures 6.5(a) - (d) and 6.6(a) - (d)).

In week 0, lateral strain values for the whole study group were typically $5 \pm 1\%$ (tension $\pm$ standard deviation) for DF motion and $4 \pm 2\%$ (relaxation) for PF motion. Principal strain values were consistently higher at $10 \pm 2\%$ for DF motion and $7.5 \pm 0.5\%$ for PF motion in week 0. Manual decompression motion achieved lower strains ($1 \pm 0.4\%$ axial strain, $0.9 \pm 0.2\%$ principal strain in week 0).

Both DF and PF motions provided mean values of lateral and principal strain that continually decreased in weeks 0-6 with the most change occurring in weeks 0-3. This

decreasing sequence of mean strain values was seen to continue to week 8 for PF motion principal strain, and through to week 24 for DF motion lateral principal strain, albeit with minimal difference in mean values in weeks 8-24. DF motion provided a reduced overlap between week-group values for lateral and principal strains.

Manual decompression mean strains decreased noticeably in weeks 0-3 but subsequently showed little difference and had large week-group overlap (figures 6.7(a) and (b)). Reciprocal of strain values had similar (but inverted) mean value trends to those described for strain but with increasing variation in later weeks, an effect that was less pronounced for principal strain values.

Cross-sectional area changed little in weeks 0-8 and then steadily increased up to week 24 (figure 6.8(a)). Mean values of CSA were typically 100mm^2 measured by assuming a circular cross-sectional area from the sagittal plane and approximately 150mm^2 measured from the transverse plane in the same time period. Final mean values of CSA for the patients were 193mm^2 and 235mm^2 for the sagittal and transverse plane measurements respectively. Sagittal and transverse plane measurements had an R^2 value of 0.72 using Spearman's rank correlation and 0.52 using Pearson's method.

The reciprocal of the product of strain and CSA did show difference over the period of healing, with mean values increasing in weeks 1-8 for both DF and PF motions and with lateral and principal strain measures (figures 6.5(e), 6.5(f), 6.6(e), and 6.6(f)). Variation in the measures increased substantially over this time, and minimal values of these metrics remained within the range of values found in patients at 0 weeks since rupture. Weeks 8-24 experienced no continuing trend in mean values with large amounts of overlap between measures from different weeks. In weeks 8-24, use of principal strain provided noticeably smaller amounts of variation within week-groups and slightly greater shift in minimal values.

Strain divided by CSA results had continually declining values for DF and PF motions with use of both lateral and principal strains, and with a more noticeable difference in weeks 8-12 using principal strain, particularly for DF motion (figures 6.5(g), 6.5(h), 6.6(g) and 6.6(h)). Week-group variation became reduced over the monitored period and was consistently less for DF motion than PF motion.

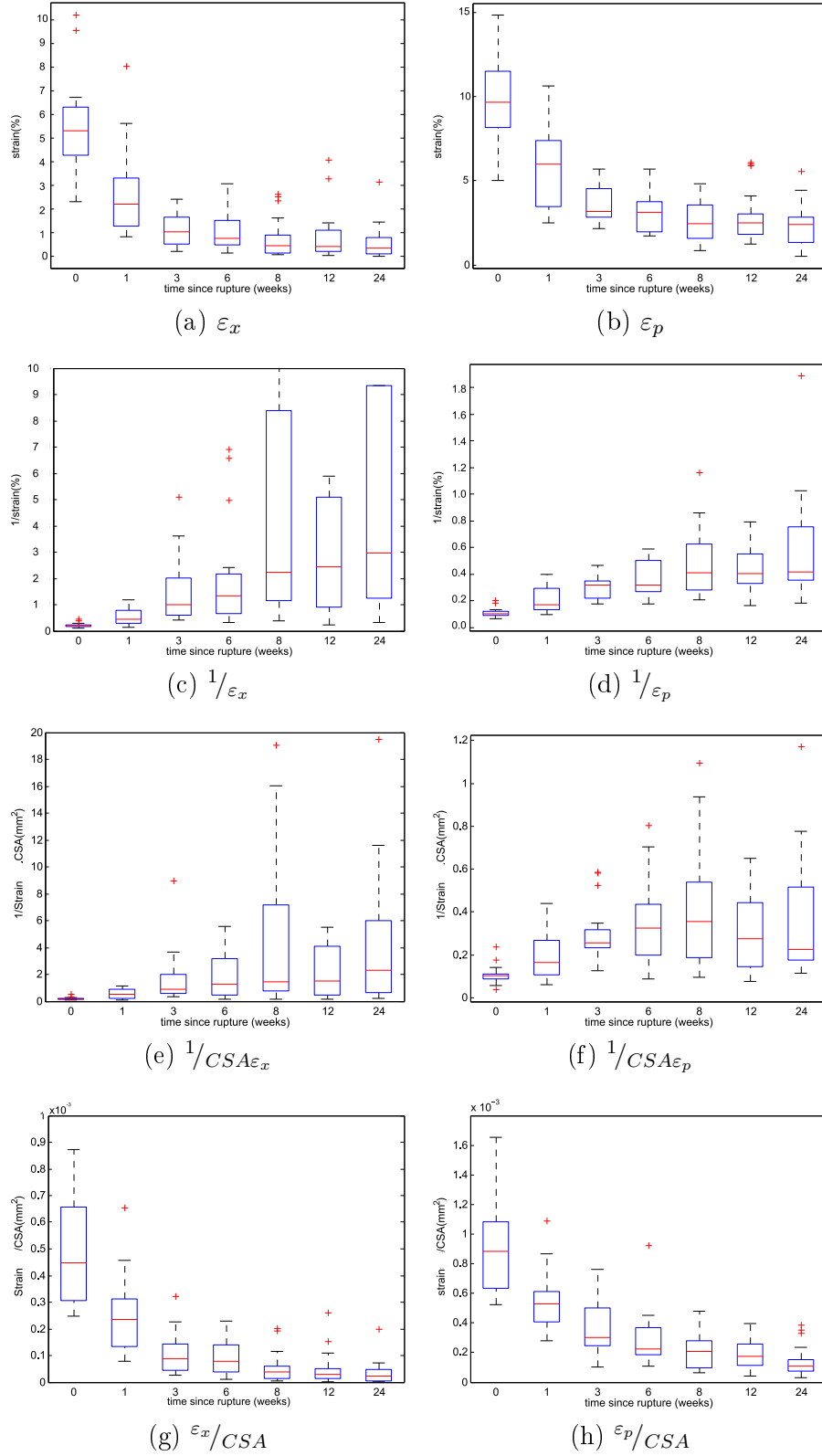


Figure 6.5: Mean elastography strains in Achilles tendon for patients against time since rupture in weeks with DF motion: (a) Lateral strain (ε_x). (b) Principal strain (ε_p). (c) Inverse lateral strain ($1/\varepsilon_x$). (d) Inverse principal strain ($1/\varepsilon_p$). (e) Inverse lateral strain multiplied by cross-sectional area ($1/\varepsilon_x.CSA_s$). (f) Inverse principal strain multiplied by cross-sectional area ($1/\varepsilon_p.CSA_s$). (g) (ε_x/CSA_s). (h) (ε_p/CSA_s).

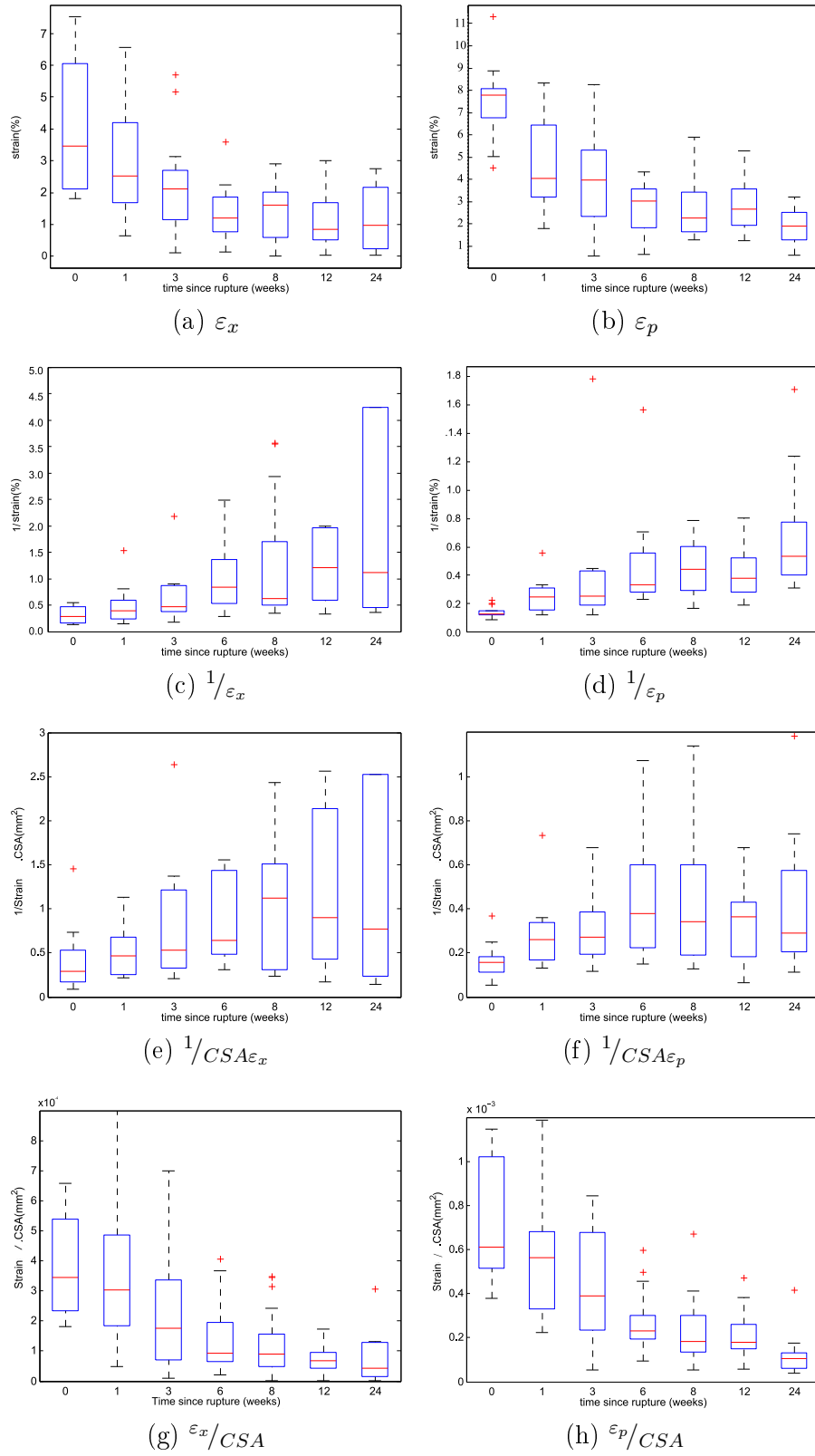


Figure 6.6: Mean elastography strains in Achilles tendon for patients against time since rupture in weeks with PF motion: (a) Lateral strain (ε_x). (b) Principal strain (ε_p). (c) Inverse lateral strain ($1/\varepsilon_x$). (d) Inverse principal strain ($1/\varepsilon_p$). (e) Inverse lateral strain multiplied by cross-sectional area ($1/\varepsilon_x.CSA_s$). (f) Inverse principal strain multiplied by cross-sectional area ($1/\varepsilon_p.CSA_s$). (g) (ε_x/CSA_s). (h) (ε_p/CSA_s).

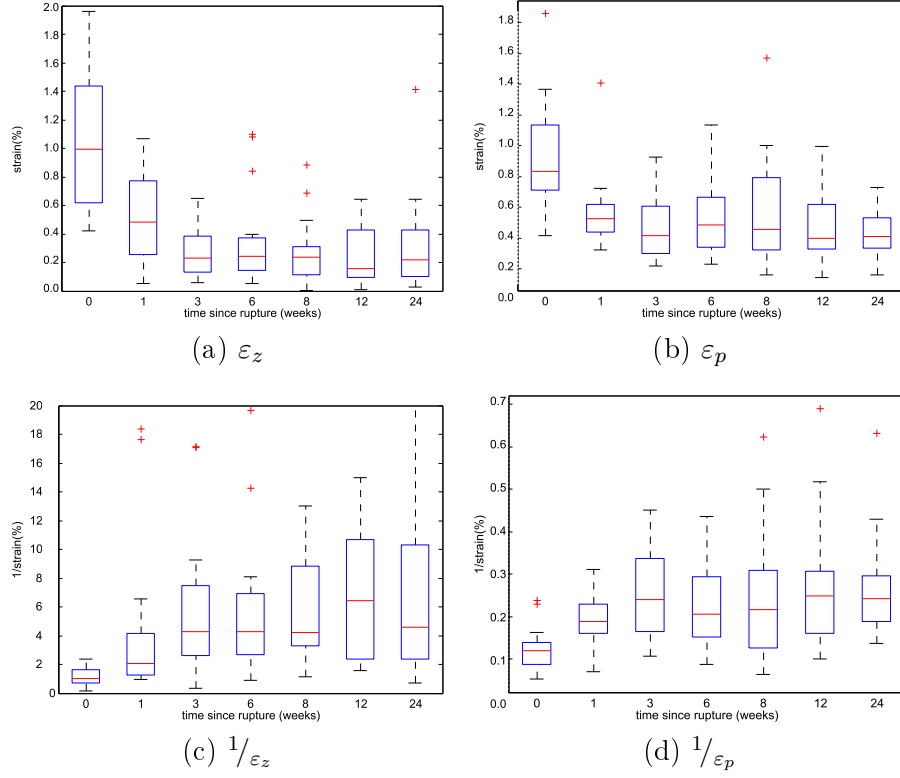


Figure 6.7: Mean strains estimated from elastography in Achilles tendon performing manual decompression motion for all patients against time since rupture in weeks: (a) Image-axial strain (ε_z). (b) Principal strain (ε_p). (c) Inverse image-axial strain ($1/\varepsilon_z$). (d) Inverse principal strain ($1/\varepsilon_p$).

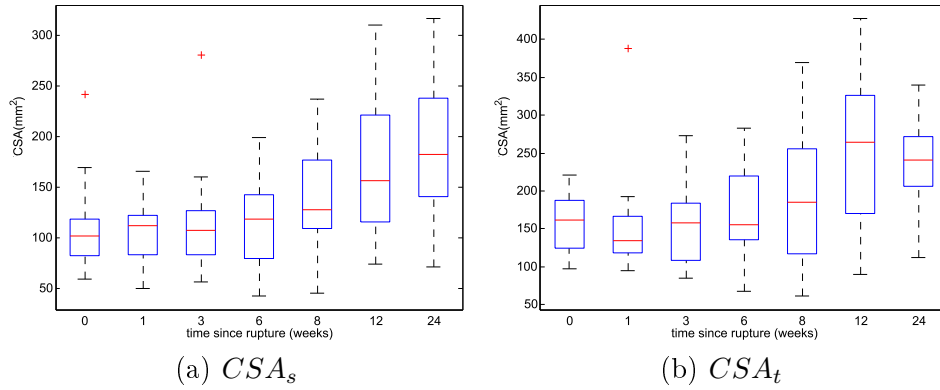


Figure 6.8: Mean tendon cross-sectional area estimated from ultrasound B-mode images for all patients against time since rupture in weeks: (a) Cross-sectional area estimated from sagittal plane measurement. (b) Cross-sectional area estimated from transverse plane measurement.

6.6.4 Results: Strain image signal to noise ratio

Imaging signal to noise ratios for strain fields (figure 6.9) were generally consistent across the duration monitored. Lateral strains for DF and PF motion produced the lowest SNRs and these slightly decreased over the duration monitored and the range of SNR. At all weeks there were strain images which had lateral strain signal to noise ratios < 1 .

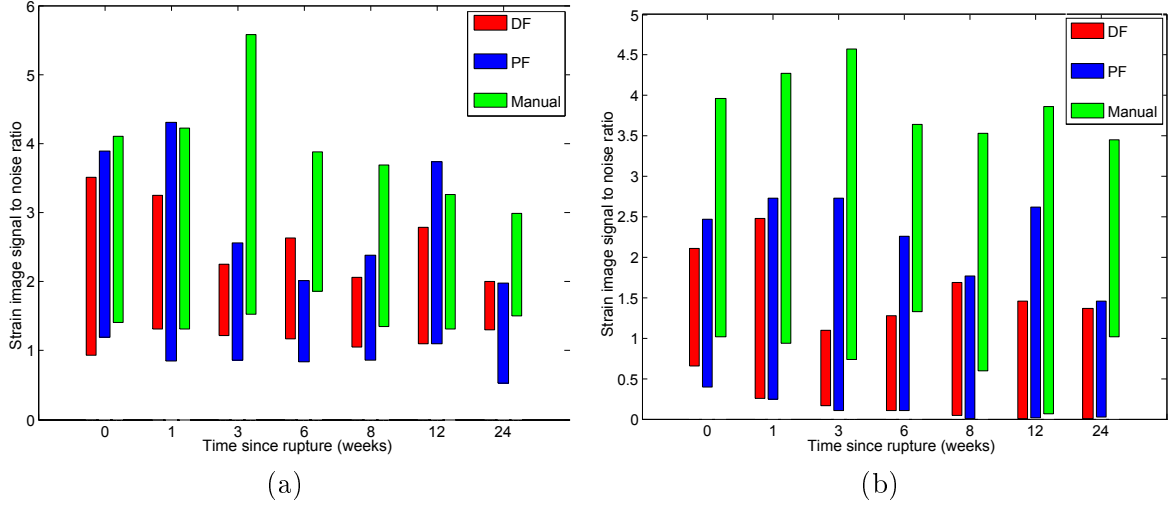


Figure 6.9: Range of signal to noise ratio of the strain images experienced with DF, PF and manual decompression: (a) Principal strain image signal to noise ratios. (b) Lateral strain image signal to noise ratio (axial strain for manual motion).

Axial strain for manual decompression were consistently higher, with both higher maximum values and higher minimal values and fewer strain images with $SNR < 1$ and the range of strain image SNRs was still high with a maximum value of 4.5.

Principal strain measurements had higher minimal and maximum strain image SNR values for DF and PF motion and had similar SNR values to axial strain for manual decompression. PF motion provided both higher and lower SNR values than DF motion. Average principal strain SNR values were still higher for manual decompression than for DF and PF motion but with a greater overlap than for the lateral/axial strain SNR.

6.6.5 Results: Repeatability

The standard deviations of each measure (table 6.3) were used to compare the motion types. DF motion has consistently lower standard deviation than the other motions, with the exception of the reciprocal of principal strain, which had less variation with manual compression/ decompression. The coefficient of variation repeatability results (table 6.4) showed that PF or DF motion had stronger responses than the manual motion. Principal strain had the highest coefficient of variation for all motion types investigated, with a maximum value of 16.02 (24.09dB) for principal strain measured with dorsiflexion (DF) motion.

Parameter	Dorsiflexion standard deviation	Planter flexion standard deviation	Manual decompression standard deviation
ε_p	0.0107	0.0138	0.0163
ε_x	0.0068	0.0105	0.0084
ε_z	0.0048	0.0090	0.0161
$1/\varepsilon_p$	1.92×10^3	6.08×10^3	0.69×10^3
$1/\varepsilon_x$	3.09×10^3	3.03×10^3	4.51×10^3
$1/\varepsilon_z$	2.60×10^3	7.78×10^3	5.04×10^3

Table 6.3: *Standard deviations from repeated measurements of subjects.*

Parameter	Dorsiflexion CoV	Planter flexion CoV	Manual decompression CoV
ε_p	16.02	9.80	10.17
ε_x	6.35	7.76	2.05
ε_z	1.71	5.07	9.01
$1/\varepsilon_p$	0.117	0.149	0.089
$1/\varepsilon_x$	0.061	0.750	0.388
$1/\varepsilon_z$	0.424	0.049	0.026

Table 6.4: *Coefficients of variation of metrics for repeated measurement of subjects.*

6.6.6 Results: Responsiveness

Responsiveness tests provided mean p-values of week-groups tested against each other (table 6.5) including all results and with outliers removed. Only one metric returned a $p < 0.05$ result which was for the principal strain divided by the cross-sectional area with outliers removed for DF motion ($P = 0.044$), and the same parameter without outliers removed gave the next best results for DF and PF motion. The other metrics that provided good results were principal strain (DF, PF), lateral strain (DF only) and reciprocal principal strain (DF, PF). Responsiveness of the CSA measures was best for sagittal plane measurement with outliers removed, but was still comparatively poor ($P = 0.125$). Both VISA-A and ATRS clinical scores gave $p < 0.05$.

ANOVA results for all groups, metrics and motions returned $P \ll 0.01$. This indicates that at least one group rejects the null hypothesis that the results are the same as all other weeks.

Parameter	Dorsi-flexion	Dorsi-flexion (outliers removed)	Planter flexion repeatability	Planter flexion (outliers removed)	Manual decompression	Manual decompression (outliers removed)
ε_p	0.129	0.106	0.134	0.071	0.328	0.285
ε_x	0.201	0.103	0.215	0.153	0.245	0.322
ε_z	0.210	0.138	0.162	0.114	0.343	0.215
$1/\varepsilon_p$	0.070	0.100	0.215	0.088	0.321	0.293
$1/\varepsilon_x$	0.324	0.126	0.4064	0.1706	0.568	0.249
$1/\varepsilon_z$	0.509	0.157	0.526	0.124	0.3372	0.168
CSA_s	0.194	0.125	-	-	-	-
CSA_t	0.360	0.274	-	-	-	-
$1/CSA_s \cdot \varepsilon_p$	0.262	0.188	0.305	0.320	0.356	0.252
$1/CSA_s \cdot \varepsilon_{x;z}$	0.350	0.317	0.426	0.237	0.493	0.381
ε_p/CSA_s	0.060	0.044	0.067	0.071	0.167	0.103
$\varepsilon_{x;z}/CSA_s$	0.124	0.071	0.136	0.104	0.285	0.110
VISA-A score	0.04					
ATRS score	0.02					

Table 6.5: Table of responsiveness of the different image derived metrics to changes over time, described by mean week-to-week student *t*-test *p*-value. Values of 0.1 or less have been highlighted in **bold**. Responsiveness of VISA-A and ATRS have also been included for reference.

6.6.7 Results: Correlation

Correlation coefficients were found against the metrics and the clinical measures for comparison (Table 6.6). The majority of the parameters gave a poor Spearman's correlation of <0.7 against time or against clinical parameters. Correlation scores were generally highest compared to time since rupture, next highest against the VISA-A clinical score and lowest against the ATRS clinical score. The best correlations were for principal strain divided by CSA for DF motion (0.85 against time, 0.80 against VISA-A score), closely followed by the same metric for PF motion (0.85 against time, 0.73 against VISA-A score). Lateral strain divided by CSA provided similar (but lower) results for DF motion and were substantially lower for PF and manual decompression. Principal and lateral strain metrics correlated moderately well with time for DF motion ($p>0.7$) and similar values for reciprocal of strains. PF motion provided similar correlation for principal strain, but far lower correlations for lateral strain and reciprocal of strain values. Principal and lateral

strain values correlated less well against clinical scores for DF and PF motions. Manual decompression motion usually provided poorer correlations than DF and PF motion and were never higher than 0.67. CSA measures correlated poorly (<0.56) and were slightly better correlated for sagittal plane measures than for the transverse plane.

	Week			VISA-A			ATRS		
Parameter	DF	PF	MC	DF	PF	MC	DF	PF	MC
ε_p	0.72	0.71	0.47	0.64	0.67	0.65	0.40	0.64	0.40
ε_x	0.72	0.60	0.59	0.69	0.48	0.48	0.41	0.50	0.53
ε_z	0.62	0.68	0.40	0.53	0.59	0.50	0.40	0.59	0.32
$1/\varepsilon_p$	0.75	0.67	0.40	0.67	0.63	0.66	0.35	0.64	0.37
$1/\varepsilon_x$	0.69	0.58	0.48	0.62	0.52	0.43	0.45	0.60	0.50
$1/\varepsilon_z$	0.60	0.62	0.33	0.50	0.58	0.60	0.35	0.59	0.32
CSA_s	0.56	-	-	0.53	-	-	0.56	-	-
CSA_t	0.44	-	-	0.36	-	-	0.44	-	-
$1/CSA_s.\varepsilon_p$	0.37	0.34	0.11	0.40	0.33	0.40	0.02	0.36	0.09
$1/CSA_s.\varepsilon_x$	0.33	0.35	0.09	0.03	0.37	0.051	0.29	0.33	0.05
ε_p/CSA_s	0.85	0.85	0.61	0.80	0.73	0.73	0.60	0.73	0.59
ε_x/CSA_s	0.80	0.68	0.66	0.73	0.56	0.56	0.56	0.59	0.53
VISA-A score	0.88			-			0.90		
ATRS score	0.90			0.90			-		

Table 6.6: Spearman rank correlation of image derived metrics (outliers $> 1.5\sigma$ removed) against time since rupture (week), VISA-A score and ATRS score for dorsiflexion (DF), planter flexion (PF) and manual decompression (MC). Values of 0.7 or greater have been highlighted in **bold**. The correlations of the VISA-A and ATRS scores against time since rupture and each other have also been included for reference.

6.6.8 Results: Patient group discrimination

Patient groups were small (10 or 11 subjects each) and results can only be taken as indicative. VISA-A and ATRS scores indicate that the PRP group was similar to the control groups in weeks 0-3 and then recovered faster in weeks 6-12 and ended up similar by week 24, whereas there was no significant difference between surgically and non-surgically treated patients (figure 6.10(c)).

Distinctiveness of measurements between groups at each time point were inconclusive for all metrics and motions when compared by t-test. For DF motion there was some indication that PRP vs. control groups were distinct in week 6 ($P < 0.05$) for principal strain and principal/lateral strain divided by CSA (table 6.7) and were more similar at all other time points (figure 6.10(a)). The metric values indicated that the PRP group was an

improvement upon the control group. CSA measurement showed groups were distinct in weeks 1 and week 6 with higher CSA values for PRP group at both of these times (figure 6.10(b)). Welch's t-tests between surgical and non-surgical groups indicated similar levels of group differences, with the most disparity in weeks 1 and 6.

Metric	Week 0	Week 1	Week 3	Week 6	Week 8	Week 12	Week 24
ε_p	0.22	0.34	0.16	0.01	0.40	0.73	0.68
ε_x	0.16	0.75	0.51	0.11	0.78	0.32	0.39
CSA_s	0.60	0.01	0.80	0.01	0.12	0.52	0.56
$\frac{E_p}{CSA_s}$	0.01	0.36	0.46	0.03	0.17	0.44	0.79
$\frac{E_x}{CSA_s}$	0.02	0.54	0.18	<0.01	0.94	0.42	0.57

Table 6.7: Welch's t-test results of PRP vs. control groups at different times since rupture.

6.7 Discussion

This study has provided important insights into the use of elastography as a quantitative measure for healing in Achilles tendons, providing for the first time a comparison of manual decompression, plantar flexion and dorsiflexure passive motion as a stimulus motion using a novel block matching algorithm to generate strain images and quantitative strain values. These results provide a level of validation for the use of these techniques and also serve as the basis for further development of both image analysis methods and for clinical protocols to provide improved performance in the future.

6.7.1 Strain measures

Strain and reciprocal of strain metrics can clearly be seen to be quantitatively responsive across the group over the healing time for the whole group of patients.

In terms of face-value image quality, the manual compression axial strain images are the most appealing. There is a clear change in strain intensity in the early weeks since rupture and the rupture zone is more clearly defined as a high strain region compared to surrounding tissue. In later image sequences (6+ weeks) this becomes less clear. This may be due to the amount of compression applied being too low to stimulate the tissue, that the variation in input force is greater than that due to the tissue-composition changes,

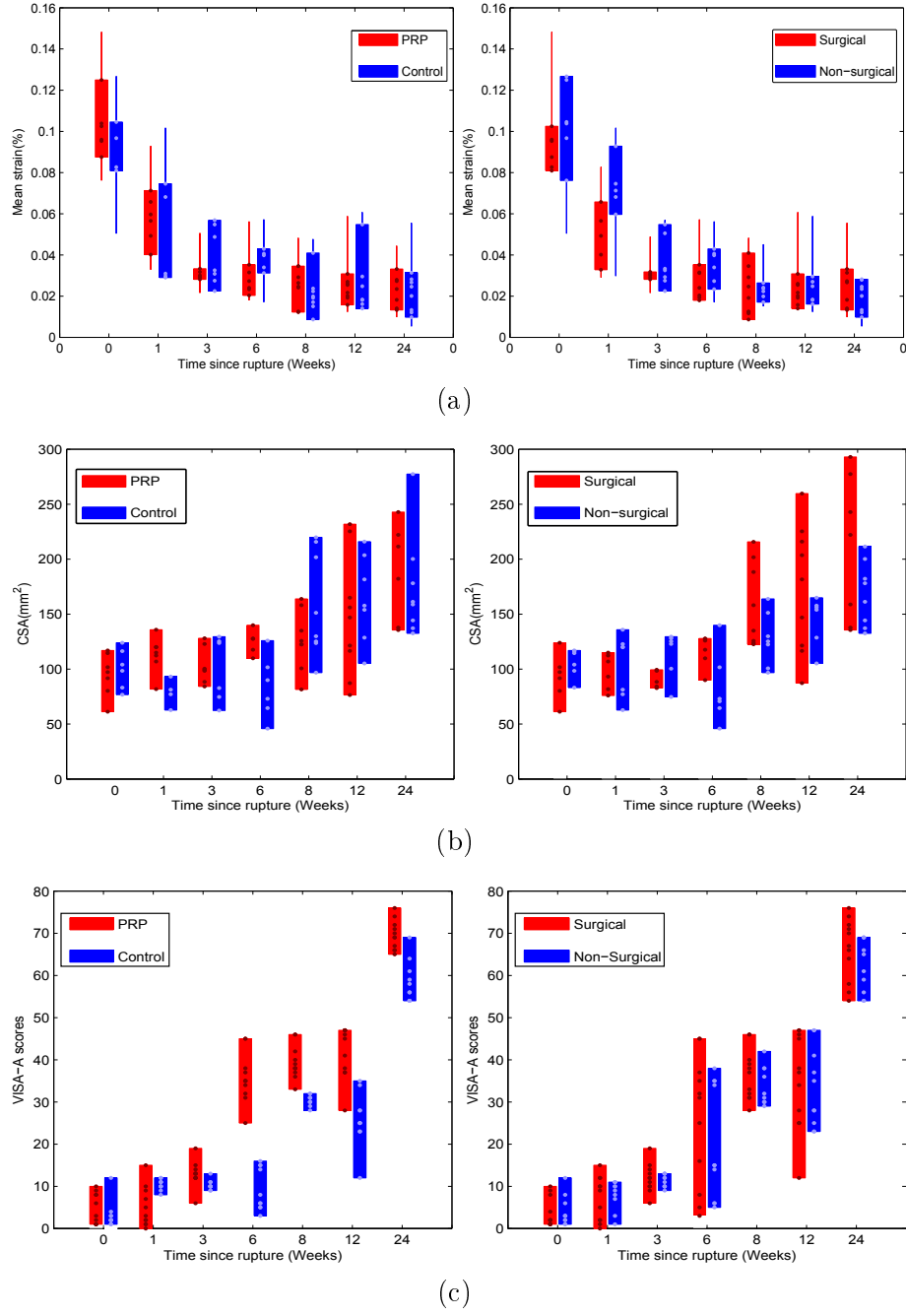


Figure 6.10: *Progress of patients with tendon rupture. Patients are subdivided between those treated with PRP or placebo (left) and those treated with surgical intervention or not (right). Solid colour bar indicates the range of results with outliers removed. (a) Mean principal strain measured by elastography with DF motion. (b) Cross-sectional area measured from sagittal plane. (c) VISA-A clinical scores.*

or because those changes are principally structural and occur in the tendon-longitudinal direction which is not stimulated. The quality of lateral and principal strain images from DF and PF motion are notionally of lower quality with discontinuities due to erroneous tracking or out of plane motion, often leading to apparent negative strains within the region of interest. These discontinuities are even more apparent in the tissue that is

deeper than the Achilles tendon, which could be due to signal path-dependence upon texture, tissue deformation and out of plane motion.

Quantitatively, the pattern of local negative strain should be compensated for by selecting a wide region of interest and may explain why results for controlled PF and DF motion provide more repeatable results than manual decompression despite the lower image signal to noise ratio which would suggest that they are more susceptible to variation in ROI selection.

In assessing the response of individuals, it is difficult to truly assess the responsiveness and specificity of strain measurement due to a lack of ground truth. Principal and lateral strains provided the best correlation against VISA-A scores and these were all below $\rho=0.70$. This should not be taken as a complete failure though: the VISA-A score was validated for end results of patients suffering rupture, not for responsiveness along progress. For this study, overall results showed that VISA-A score was more responsive and better correlated against time than any of the strain results derived here. However, when the response of individuals is considered, it can be seen that the VISA-A score is less responsive between weeks 0-1 of healing and that for patient 6 it failed to return a significantly different score despite the subject re-rupturing their tendon (figure 6.11). By contrast, the principal strain and lateral strain values showed a high response to re-rupture, although there was no clear indication that strain results could have been predictive of the re-rupture (figure 6.12).

Repeatability of measurements was shown of the different motion types and various strain metrics with both a simple measure of the standard deviation of repeated measurements and by a normalised measure, the coefficient of variance. The standard deviation test demonstrated that for the basic and principal strains, the controlled motion DF and PF motion consistently outperformed the manual compression method, a finding that this author has previously presented at a conference with results found by a multiscale block matching algorithm [177] and reconfirmed here with the AutoQual algorithm. Despite the additional complexities of motion, additional potential image artefacts and lower image SNR, the advantage from controlling the deformation of material in a more repeatable manner means that more consistent quantitative results can be achieved from controlled

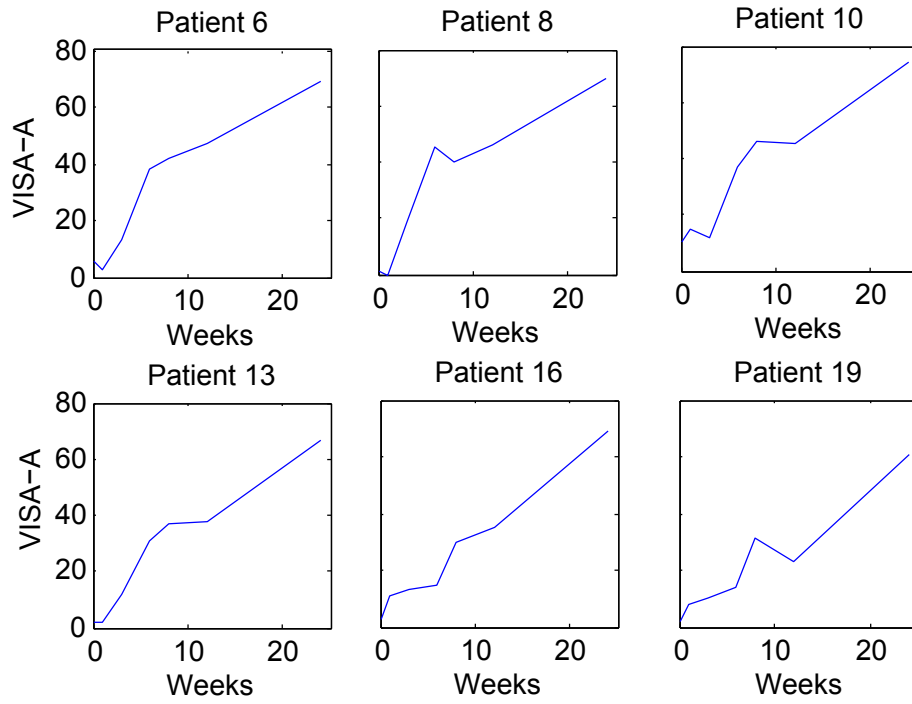


Figure 6.11: *The responses of individual subjects' VISA-A score over time since rupture. Note that Patient 6 suffered a re-rupture of the Achilles tendon between weeks 8 and 12, yet there is no clear response in VISA-A score compared to that experienced by the other subjects.*

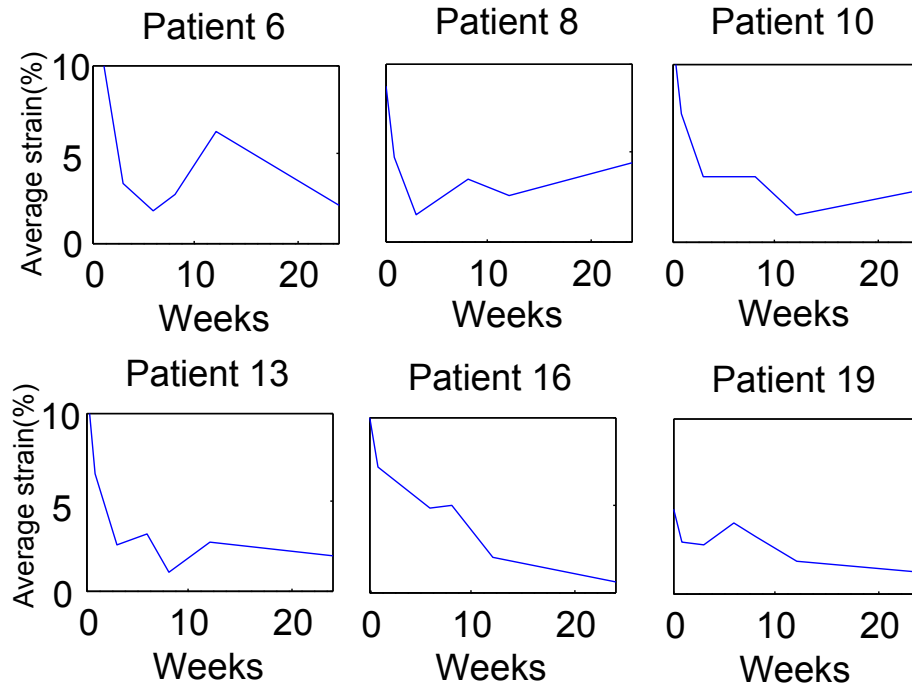


Figure 6.12: *The responses of individual subjects' mean principal strain at rupture site over time since rupture. Note that Patient 6 suffered a re-rupture of the Achilles tendon between weeks 8 and 12, and that there is a clear response compared to other patients.*

flexion. That the DF motion was more repeatable than the PF motion is also a useful finding - here, the tendon is being stretched in its functional direction, whereas the PF motion effectively slackens the tendon and may be susceptible to more variation as the

subject may be inclined to flex the muscles in the lower leg to compliment the motion of the foot. Note that this finding may not be applicable to alternative methods that use voluntary muscle contraction rather than passive motion as used in this study.

In the coefficient of variance test, principal strain outperformed the axial or lateral strain measures, achieving a maximum CoV of 16.02 for principal strain with DF motion. DF motion greatly outperformed PF or manual motion for principal strain metrics and PF motion performed better than DF motion otherwise. DF and PF both out-performed manual compression for lateral strain measurement and manual strain had the highest CoV for axial strain which is all as expected.

Taking the reciprocal of the strain substantially lowered the CoV and repeatability, as the numbers calculated are smaller than 1 and very small strains are found in later weeks, meaning that a small variation can lead to a large variation in reciprocal of strain and higher noise (figures 6.5(a)&(d), 6.6(c)&(d), 6.7(c)&(d)). While taking the reciprocal makes sense as being proportional to the tissue stiffness (assuming repeatable force, motion and constant cross-sectional area), it was concluded that it does not accentuate differences in mean values between weeks for later stages of healing as the repeatability of individual experiments has decreased too much.

The CoV as used here is not as strong an indicator of performance as would be desired. The low number of repeats per experiment (2 or 3) means that there could be a substantial error in the mean value calculated, adversely affecting the results. The results for CoV should therefore be interpreted as indicative and in support of other results rather than conclusive (and hence the need to include the more simple repeatability results which can be used for comparing motion types but not different strain metrics).

The student t-test for responsiveness between weeks reinforced the general findings of the repeatability experiments. DF and PF motions outperformed manual decompression for all parameters except for the inverse of axial strain, and that measure was poor ($P=0.34$ for manual decompression). Lateral strain, principal strain, and inverse principal strain measures all scored $P \leq 0.1$, demonstrating that they are somewhat responsive to changes in the groups week on week, although it should be noted that lateral strain was more positively affected by outlier removal than principal strain or inverse principal strain.

This finding is understandable from looking at the box plots (figure 6.7) where it is clear that there are some significant changes in mean value in weeks 0-3 (but with substantial overlap of distribution) and no major change thereafter. For principal strain with DF motion, the decreasing trend in mean values remains visible for strain measured with DF motion up until week 8.

Spearman correlation tests against time since rupture showed moderately good correlation ($\rho > 0.72$) for lateral and principal strain measured with DF motion and it is clear that this correlation coefficient would be higher if just the first 8 weeks were accounted for (up to $\rho > 0.77$ for principal strain, DF motion). Spearman correlations against the clinical metrics are less good, with $\rho < 0.70$ for all metrics and motions. This is less good than the results that Schepull et al. [111] have reported against their final outcome metrics of up to $\rho = 0.88$. These differences could be inherent to the strain measurement or final outcome scoring methods and it should be noted that the best correlated measure used by Schepull et al. measures physical capability alone [187] without accounting for pain response and patient perception (as used in the VISA-A and ATRS scores) which may make it more directly related to tendon stiffness.

Differences between using lateral strain and principal strain appear to be small, although the use of principal strain slightly outperforms lateral strain for DF and PF motion. Correlations were better with PF and DF motion compared with manual decompression for all measures which would be accounted for by the improved repeatability of this method and possibly due to improved responsiveness of the method to structural changes in the tissue as well as material changes. DF motion outperformed PF motion for almost all metrics.

Signal to noise ratios were low for lateral strains with DF and PF motion, but this was somewhat expected as small discontinuities in the displacement field can lead to local positive and negative strains and therefore high standard deviations. Care was taken in selecting tendon regions of interest to ensure wide areas which minimised the variation in mean values and which avoided areas where artefacts were present.

The findings that DF motion has better correlation with changes over time and has better responsiveness (for lateral strain) than PF motion is substantiated by findings

from other studies measuring flexion force capability, which have found that PF motion of ruptured Achilles tendons that had fully healed provided a lesser comparative difference to the unruptured leg than for DF motion [188,189]. This could be due to passive dorsiflexure being more greatly dependent on the capability of the Achilles tendon to store energy, whereas plantar flexion involves an increased amount of calf muscle function.

Attempts to discriminate between patient groups showed some indication that the PRP group experienced a reduced strain in week 6 which may indicate a faster stiffening of the tissue. The number of samples is, however, low and the variation of strain measurements between patients is high enough to cast doubt upon this finding without further investigation. It may be that there was no significant mechanical property difference in the tendon that could be measured by strain, a conclusion that would be supported by Schepull et al. who have also investigated the effects of PRP [112]. However, a recent study in rat tendons indicated that maximum strength and stiffness of tendons treated by PRP rather than saline solution were both increased 7 days after administration, which is encouraging that this strain measurement may be able to distinguish groups under the correct conditions [190].

6.7.2 Cross-Sectional Area measurement

Cross-sectional area (CSA) results were less good in terms of responsiveness and correlation than the strain results. Although it can generally be seen that the tendons become larger over the 24 weeks since rupture, the measurement is not a responsive indicator week-by-week. CSA measurement P-values (table 6.5) were no better than $P=0.13$ for the sagittal plane method and $P=0.27$ for the transverse plane method. This conforms with the findings of Ekizos et al. who found that measurement of cross-sectional areas of ligaments using ultrasound was fraught with inter- and intra-clinician variability [191].

Values for cross-sectional area measured in two different planes were substantially different, with values measured in the transverse plane being higher (mean values change from 139.3mm^2 to 255.8mm^2 for transverse plane compared with 90.5mm^2 to 179.5mm^2 for sagittal plane measures). Transverse plane measurements are of more similar values to those reported by Schepull et al. [111] and the trend of increasing values (measured at 6,

12 and 18 weeks post rupture by Schepull) is also confirmed here. It should be noted that Schepull et al. found that the CSA then dropped for most of their subjects between 18 weeks and 52 weeks post rupture, and that their method was also based upon measuring the CSA from the transverse plane of an ultrasound image. The CSA from transverse plane images is likely to be closer to the true value, as many of the images clearly showed a non-circular CSA.

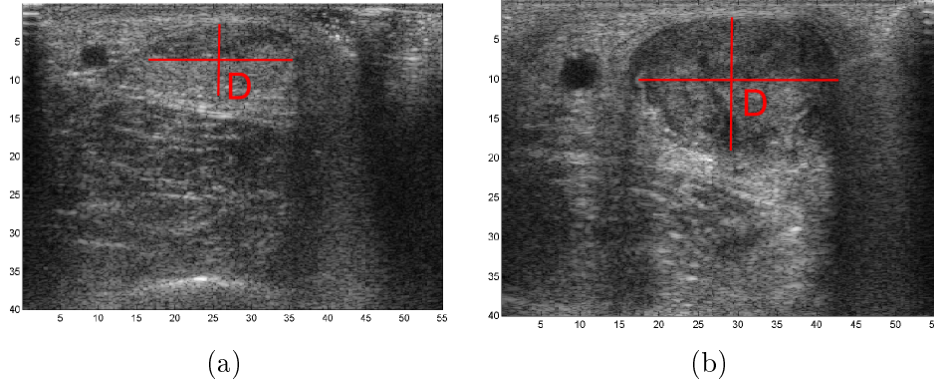


Figure 6.13: *Examples of transverse plane tendon B-mode images. ‘D’ indicates notional diameters of the tendons. (a) 1 week after rupture, distinguishing the tissue types is impossible to perform with certainty. (b) 12 weeks after rupture, the tendon is visibly larger and rounder and tissue distinction is clearer (NB: same subject as (a)).*

Sagittal plane measures also had slightly better (though still poor) Spearman correlation coefficient (0.56 sagittal, 0.44 transverse compared against time since rupture). Identifying the different tissues in the transverse plane can be difficult, especially when measured at a rupture site and in the early stages of healing (figure 6.13). Differences between patients and from the same patient over the course of healing mean that different pressures may be applied in order to ensure good acoustic contact. This can lead to differing deformation of the tendon and increases the difficulty of consistent measurement.

Ruptured and partially healed tendon can also consist of a mixture of tissues that can have different ultrasound reflectivity (figure 6.16(a)) which becomes more homogeneous as part of the healing process (figure 6.16(b)) but which can initially make accurate diameter assessment difficult. A mixture of tissue type within the partially healed tendon is consistent with histology findings from partially healed tendons [24].

In the sagittal plane however, tissue differences are somewhat easier to distinguish and acoustic contact can be maintained with a minimal pressure. The difficulty in accurately

measuring at the rupture zone in early weeks is still present: the blood clot attenuates signal and can cause a shadow, while tissue contrast between the remaining tendon and surrounding tissue often remains low (figure 6.14(a)). In situations of low contrast the elastography analysis from controlled lateral motion can be helpful as the disparity in motion of the different tissues can additionally identify the tissue boundaries. This is clear in the motion image (figure 6.14(b)) and the principal strain image (figure 6.14(c)). However, this is not a universal rule as there are many instances where the greyscale image is clearly indicative of the tissue boundary (figure 6.15(a)), but the motion image shows a level of continuity of displacement values in surrounding tissue (figure 6.15(b)). It is not believed that this is an erroneous artefact of the displacement tracking algorithm and indicates a degree of motion continuity in surrounding tissues. Predictably, there are also cases where there is both poor greyscale B-mode and no clear motion discontinuity to indicate tissue boundaries, reducing the certainty of tendon diameter measurement.

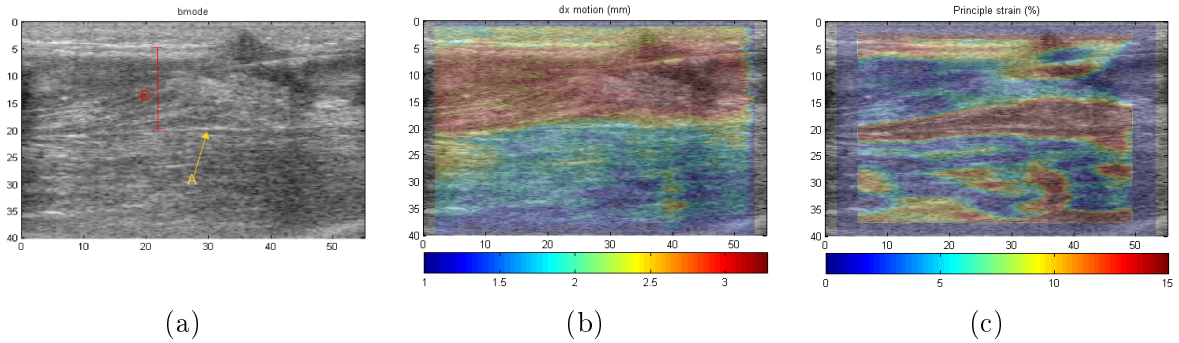


Figure 6.14: *Example of sagittal plane tendon image (6 weeks post-rupture) with low greyscale contrast to illustrate the difficulty of measuring the tendon diameter: (a) B-mode image, ‘D’ shows the notional diameter, ‘A’ shows a bright layer that may indicate the tendon boundary (b) Image-lateral displacement image generated from motion sequence with passive dorsiflexion motion, the disparity of motion indicates the tissue boundaries. (c) Principal strain image generated from the same sequence. The shear strain of the motion at the tissue boundary gives a high response.*

All of these issues not only make the manual measurement of post-ruptured tendon cross-sectional areas difficult, they also make it hard to foresee a reliable automated method for measurement or segmentation of these areas.

For Spearman correlation tests, CSA was poorly correlated against time and clinical metrics were substantially below those correlations for principal or lateral strain with PF and DF motion and were usually well below those found for axial strain with manual

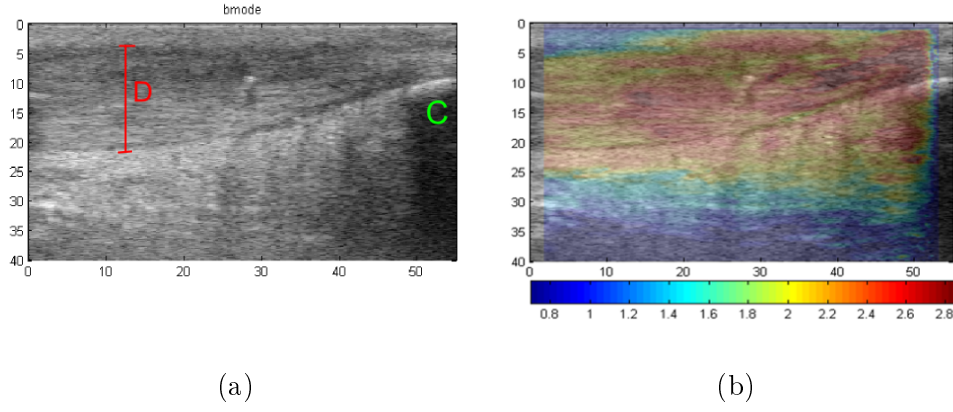


Figure 6.15: *Example of sagittal plane tendon image (12 weeks post-rupture) with good greyscale contrast between tendon and surrounding tissue but poor disparity of motion between tissues to illustrate the difficulty of measuring the tendon diameter: (a) B-mode image, ‘D’ shows the notional diameter, ‘C’ shows the calcaneus. (b) Image-lateral displacement image generated from motion sequence with passive dorsiflexion motion.*

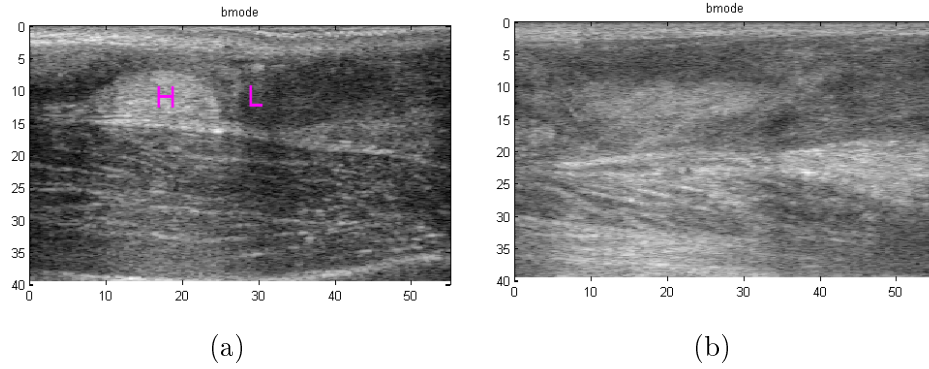


Figure 6.16: *Examples of sagittal plane tendon B-mode images (a) 1 week after rupture, ‘H’ shows high signal response tissue region within the tendon, ‘L’ shows low signal response region. (b) 12 weeks after rupture, some disparity is still visible but signal response is more homogeneous (NB: same subject as (a)).*

motion as well.

It is concluded that CSA alone is a poor indicator of tendon rupture progress, being less repeatable, less responsive and less well correlated with progress against time or clinical outcome measures than measurements of strain using ultrasound elastography. Where CSA measurement is required, sagittal plane scans should be used to take account of their slightly better correlation and responsiveness to changes over time, but that these should be calibrated against a rigorously measured cross-section measurements, possibly from 3D nMRI studies or by using gel pads to maintain acoustic contact for ultrasound imaging without compressing the tendon.

6.7.3 Combinations of strain and CSA metrics

Combining the strain measures with the cross-sectional area measure affected the responsiveness and correlation results greatly, and in an unexpected manner. The results for the Young's modulus (assuming repeatable force) measure were not good, with the additional noise from the CSA metric confusing the picture and leading to a responsiveness of $P=0.19$ and Spearman correlations of <0.40 . It is clear that, although a mean shift in the group values is visible, that the main effect was to increase the variation within the week-groups, particularly for later results.

However, the principal or lateral strain divided by the CSA provided the best responsiveness results of all, $P=0.044$ and $P=0.071$ for DF and PF motions respectively with outliers removed, making the results on average to be significantly different from each other. This is surprising, as this does not appear to be a direct property of interest. However, given that it is shown that the strain experienced from the repeatable flexion of the ankle goes down over the period studied, and that the CSA increases, then this combination is the most complementary to being responsive to changes over time, as shown in figure 6.5(h). The response of strain to time is also strongest in weeks 1-8, and the response to CSA is strongest in weeks 8-24, meaning that the results complement the insensitive response times of each other.

The Spearman correlation test also gave similar insights for these combined measures. In nearly all cases the parameters investigated correlated better against time since rupture than against the VISA-A or ATRS results (manual motion principal strain divided by CSA provided a better result correlated against the VISA-A score than against time since rupture). These results can be considered well correlated against both time and VISA-A score, and are comparable to results found by Schepull et al. for modulus values compared to their final outcome metrics.

As with the responsiveness analysis, the measure of strain divided by CSA provided the best results. Correlation coefficients were approximately $\rho=0.5$ for principal strain divided by CSA with either PF or DF motion, and up to $\rho=0.80$ for DF motion compared with VISA-A score. This is a significant finding, that combining controlled motion strain measurement and cross-sectional area measurements can increase responsiveness and cor-

relation to a clinical metric compared to any one measure alone. However, this improved responsiveness did not translate into an increased ability to discriminate between different patient groups to any greater effect than with CSA or strain values alone for this study.

6.8 Conclusions

This chapter has assessed the capabilities of using *in vivo* strain measurements of Achilles tendons with controlled passive flexion of the foot and ankle in order to measure changes in material properties in the functional direction.

The main findings are:

- Controlled plantar and dorsiflexure motions can produce more repeatable lateral-strain measurements than axial-strain measures from manual decompression.
- Images of lateral or principal strain can show high value regions in the first 1-3 weeks post rupture.
- Quantitative principal and lateral strains from controlled dorsiflexure passive motion can be responsive to property changes up to 8 weeks post rupture, and that these measures are more responsive than those found by manual decompression.
- Changes in strain values from controlled dorsiflexion are more strongly correlated against time or clinical metrics than manual decompression.
- Tendon cross-sectional area measurements are difficult to take in a robust way and care needs to be taken to ensure accuracy.
- Combining strain with CSA measures can increase the responsiveness of the measure by benefiting from the regions of each metric that are responsive to changes at different points in the healing process.
- Strain measurements, CSA measurements and combinations of both did not help significantly discriminate between different patient groups.

These findings need to be built upon, with developments of better protocols to enable higher strains to be produced in stiffer tendons so that signal to noise ratios of strain

images are improved. In this study motion ranges and forces were deliberately kept low in order to ensure safety of patients in early weeks, but keeping the same protocol has restricted the ability to measure strains in the functional region of the tendon in later weeks. Measurement of force, moment arm length and foot angle should also be incorporated as these should be accurately measurable and may reduce some of the variability that is seen between patients and increase responsiveness of measures. This would also allow for calculation of the tendon's Young's modulus at the rupture site.

The use of principal strain is novel and appears to provide some additional benefits to measuring strains in tendons. Care needs to be taken with this though, as this value can be highly affected by shear strains both within the tissue and from slippage at tissue boundaries. If the principal strain value is also to be used as part of material property calculations, then it should be borne in mind that it is not a measure of tensile strain and may not be directly usable for elastic modulus estimation.

Chapter 7

Artefacts in axial and lateral strain images of ruptured Achilles tendons

This chapter comprises of a discussion of some of the key strain image artefacts found during the extensive study of ruptured Achilles tendons over the course of healing. This is of importance to those wishing to interpret strain images further, as the description of strain images of Achilles tendons could be misinformed and is not well documented for lateral motions. Interpreting point values or incorrect regions of interest as being of significance could greatly distort analysis and lead to inaccurate conclusions being drawn.

Here, an artefact is defined as any area of the image where the reported or estimated strain values may not be representative of the true strain experienced by the tissue. This results in an apparent strain estimation field pattern which is not representative of the true distribution of strain in the tissue.

The artefacts are each described and mitigating strategies, either in algorithm setting, ROI selection or acquisition protocol are suggested. These artefacts are:

- Displacement precision error variation
- Bone region decorrelation
- Discontinuous tissues and slip boundaries
- Lateral tracking of shadows
- Out of plane motion
- Fast motion decorrelation

7.1 Strain pattern from displacement precision error variation

7.1.1 Displacement precision error variation strain artefact description and examples

Each block matching estimation has some inherent precision error- interpolation errors, non-linear compressions, or signal noise can all cause localised errors in the tissue displacement estimation. The result is that the displacement estimation images appear somewhat ‘noisy’¹. The distributions of unregularized displacement fields minus those with a strong 2D median filter applied post-process have been evaluated (equation 7.1, where N is the local error value, dx are the displacement estimates found by block matching, and $\widetilde{dx}$ are the 2D median filtered displacement estimates). It has been established that this variable error is largely closely centred around the median value in a sharp peak that is approximately Gaussian (evaluated by the chi squared test). This does not truly represent the error variation, only the difference to the median filtered value, but this serves to get an estimate of the behaviour of the variation in displacement estimates with real data.

$$N_{i,j} = dx_{i,j} - \widetilde{dx}_{i,j} \quad (7.1)$$

Random Gaussian precision error was then added at a signal to noise ratios of 20dB to a linear 2D displacement field (figure 7.1(c)) and then the smoothed strain field was estimated (figure 7.1(d)). Note that this is a synthesis of a displacement field with precision error similar to some seen in *in vivo* examples (an alternative strategy could be to add noise to the ultrasound image and investigate the capability of the block matching algorithm to minimise precision variation in the resultant displacement field).

The resultant strain field showed local variation patterns that could be misinterpreted as local strain quantities and therefore as patterns of interest. The maximum/ minimum strain values found by this method depend upon the signal to noise ratio input and upon the amount of smoothing applied when evaluating the strain (which also affects the

¹The term ‘noise’ has been generally avoided in order to prevent confusion with RF signal or image noise noise

width and shape of the apparent strain features). This is a part of the mechanism for increasing image signal to noise ratio from phantom experiments and artificial data, which is discussed in greater detail in chapters 5 and 8.

Similar strain patterns can be expected from noise when evaluating the strain in the axial direction (as in conventional elastography). Studies have previously commented that the local strain pattern may be of interest and could be used as a qualitative guide for evaluating tendon health [139, 152, 156, 168, 171], and it is possible that the patterns commented on may not be indicators of higher strain, but of higher variation of error.

The strain pattern from displacement estimate error variation is often noticeable in strain fields where the tissue is largely homogeneous and the strain field is otherwise smooth and homogeneous if low levels of smoothing are applied (figure 7.2). As previously found in chapter 5, altering the degree of smoothing does not significantly impact on main strain values found if a sufficiently large region of interest is selected.

7.1.2 Strain pattern from displacement local precision error artefact mitigation

The strain pattern from displacement error variation could theoretically be greatly reduced by by low pass filtering of the strain image (figure 7.1(f)) but a more thorough investigation would be required to prove that this approach is beneficial and does not overly affect mean strain values with real data.

Smoothing of the displacement field by median, Gaussian or similar 2D filtering could also reduce the effect of this artefact, as could using more robust regularisation methods or modelling (chapter 8). However, this would reduce the distinction between tissue types, although this could be somewhat accounted for by using an edge preserving smoothing technique [192]. Non-local means [193] is another method of removing noise from a signal while preserving the detail and structure of the image. This could be employed either to remove the precision error in the displacement fields or to reduce signal noise in the ultrasound RF. There are numerous image enhancement techniques which can be used to improve the quality of ultrasound images for clinical review [194]. Although these could reduce one of the sources of the displacement value precision error but it is unclear whether

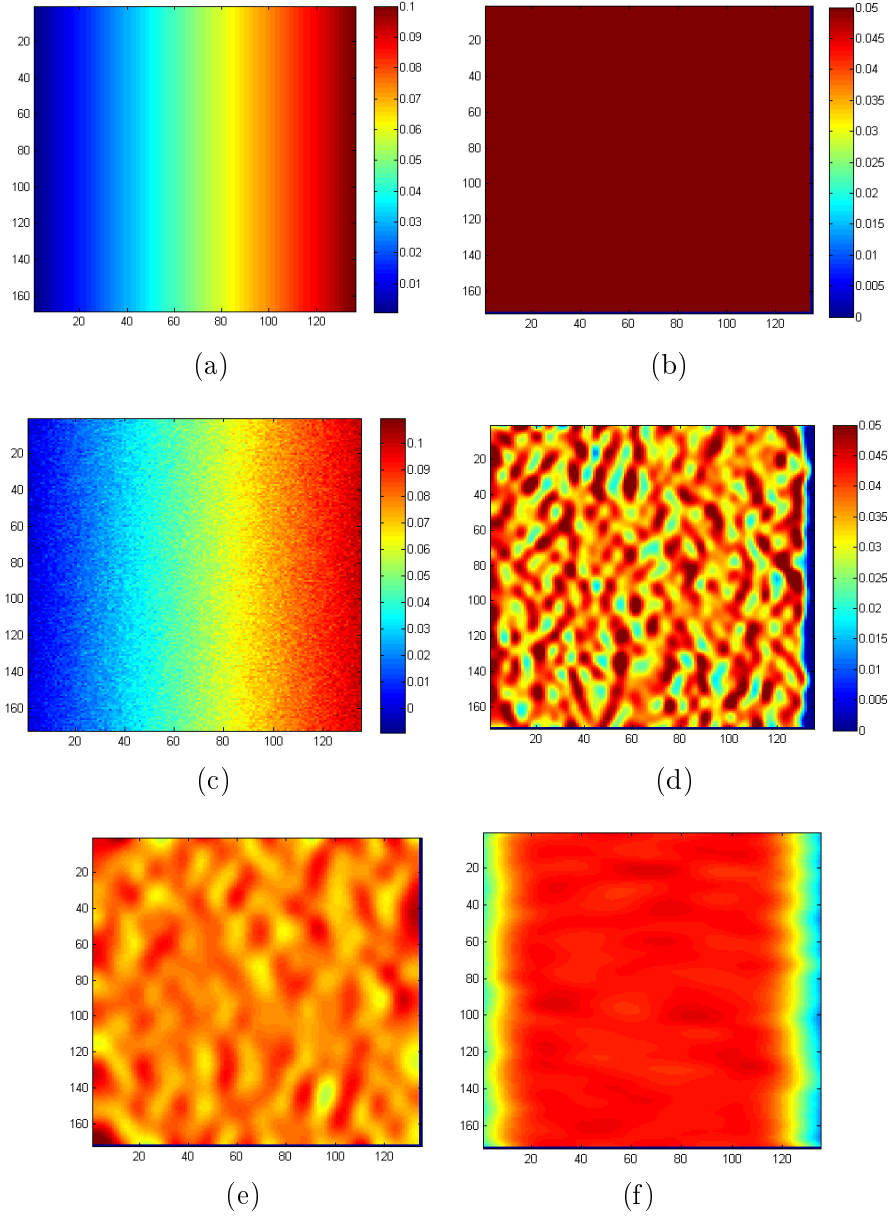


Figure 7.1: (a) Example of artificial displacement field of linear strain with no precision error. (b) Resultant uniform strain field with no precision error. (c) Example of artificial displacement field of linear strain plus Gaussian precision error. (d) Resultant ‘noisy’ strain field with minimal smoothing. (e) Resultant ‘noisy’ strain field with greater smoothing. (f) Resultant ‘noisy’ strain field with low pass filter. Note that the mean value is higher than in (d) and (e) which have identical mean strain values (identical colour scale to (d) and (f)) .

this method would also remove characteristic signal speckle which would aid displacement estimation.

Aside from regularisation or smoothing methods to reduce the appearance, performing the block matching on the frames in reverse order and then combining with the forward-run frame-by-frame displacements (either as a mean value or with some weight-

ing function) have been proposed to assist [195]. Initial experiments indicate that there is little visible improvement in using this ‘forward-and-backward’ method (figure 7.2(c)) and the doubling of computation time is undesirable.

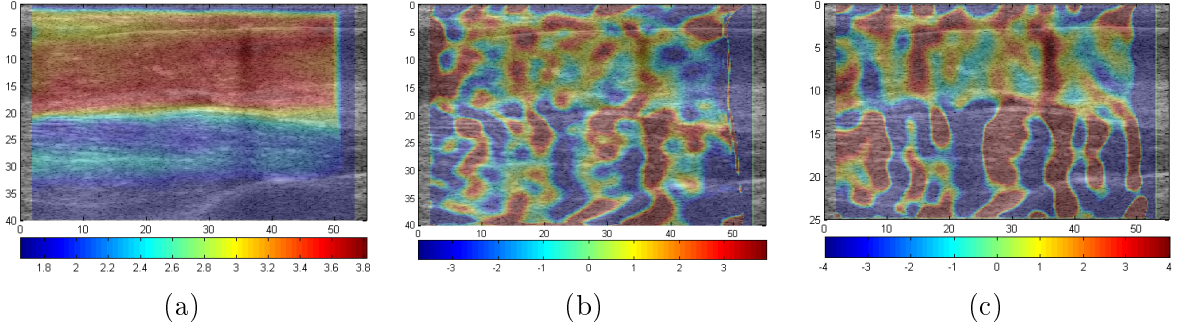


Figure 7.2: *Example of an Achilles tendon elastography analysis 12 weeks post-rupture. (a) The displacement (mm) image visibly seems very even in the tendon region. (b) The strain image (%) with minimal smoothing showed an uneven pattern with some areas of low and negative strain which is physiologically unlikely. This pattern appeared very similar to that generated by additive random error in the displacement field. (c) The strain image(%) found by performing block matching on the sequence using ‘forward-and-backward’ method. Strain pattern may be slightly more uniform at the centre of the tendon region but artefacts have become more pronounced in the deeper tissue.*

Ultimately, the best mitigation of the quantitative effect of the strain pattern variation is to ensure that a wide region of interest is selected to analyse strain. This should give the most consistent quantitative results as positive and negative strain fluctuations will average to a more stable and accurate mean value. Care should be taken to select a notionally homogeneous area of tissue.

7.2 Bone regions

7.2.1 Bone decorrelation description and examples

Images that contain calcaneus or tibia will fail to continue accurately tracking within the bone region (figures 7.3 and 7.5). Ultrasound cannot significantly penetrate bone, and any apparent image texture is caused by internal reflections within the superficial tissue. These artefacts are unlikely to affect measures of Achilles tendon strain measures, as they would not be selected as regions of interest of the Achilles tendon.

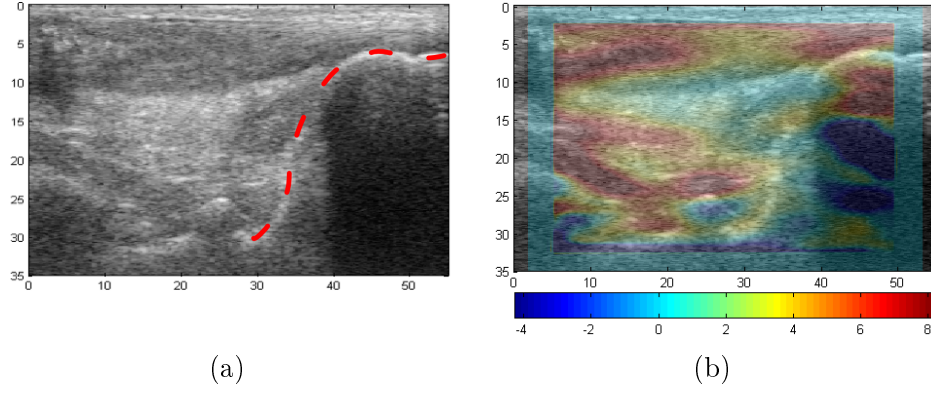


Figure 7.3: (a) B-mode image of an Achilles tendon 12 weeks post rupture that includes the calcaneus. Calcaneus boundary is shown with red dotted line. (b) Z-direction strain image (colour scale in %) where the AutoQual block matching algorithm has failed to track within the calcaneus.

7.2.2 Bone decorrelation mitigation

This is unlikely to present a problem for quantitative strain measurement of the Achilles tendon. However, lateral elastography users should note that block matching in hard tissue is not possible in an ultrasound imaging modality and therefore values from strain estimations in these regions are not valid.

7.3 Discontinuous tissues - slip boundaries

7.3.1 Slip boundary description and examples

Discontinuous motion fields arising from bodies sliding over each other can disrupt the continuity of the strain field. Specifically, at the sliding interface of two tissues each should be considered as a separate body and thus no strain is imparted at the interface between them. However, a tracking algorithm with its assumptions that the medium is continuous would assess there to be a high shear strain value between the bodies from the motion (figure 7.9).

Notable features in the area of the Achilles tendon are the interface between the Achilles and surrounding tissue, for the flexor hallucis longus (figure 7.5(b)) and surgical suture can show high apparent strain due to slip boundaries (figures 7.5 and 7.6). Interfaces to hard tissue and at the skin are also likely to be slip boundaries although this is more clear on both strain and B-mode images.

Tendons may not run truly parallel to the leg skin-surface (figure 7.7), which can lead

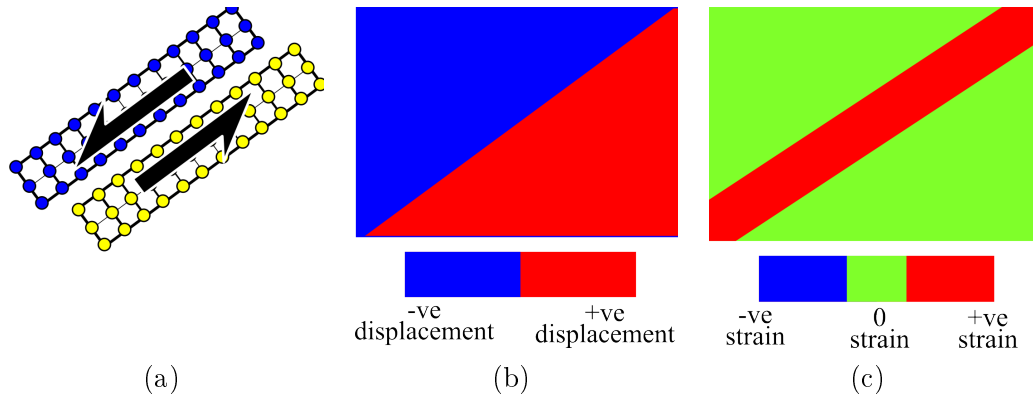


Figure 7.4: *Simplified illustrations of two unconnected bodies sliding past each other at an angle to the observed image axes. (a) Body diagram of sliding motion. (b) Illustration of lateral displacement found by block matching. (c) Illustration of resultant strain field across body boundary. The motion has shown an apparent large strain and highlights that the assumption of a continuous material can be erroneous.*

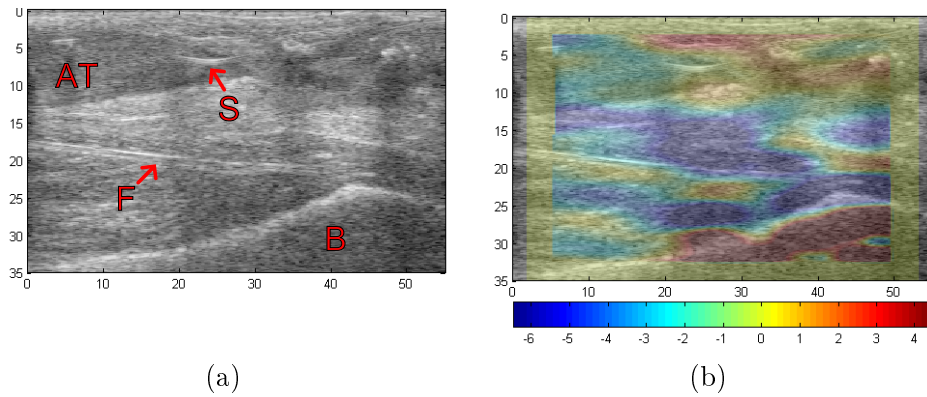


Figure 7.5: *(a) B-mode image of an Achilles tendon 12 weeks post rupture that includes the tibia. ‘AT’ is the partially healed tendon, ‘B’ is the bone region of the tibia, ‘S’ is a section of surgical suture, ‘F’ is another tendon, probably the flexor hallucis longus tendon. (b) Z-direction strain image (colour scale in %) where the AutoQual block matching algorithm has failed to accurately track within the tibia.*

both to an incorrect physiologically relevant strain being estimated (due to the assumed image-lateral strain vector not being correct) and also can suggest apparent high strain at the tendon tissue boundary due to slippage. This boundary strain could be extremely high and thus physically implausible as a continuous tissue. This mainly occurred in early weeks where swelling of surrounding tissue was more significant, although patient fat levels could also be a factor. Theoretically, the principal strain should be unaffected by this as the principal strain direction does not have to be parallel to an arbitrary axis.

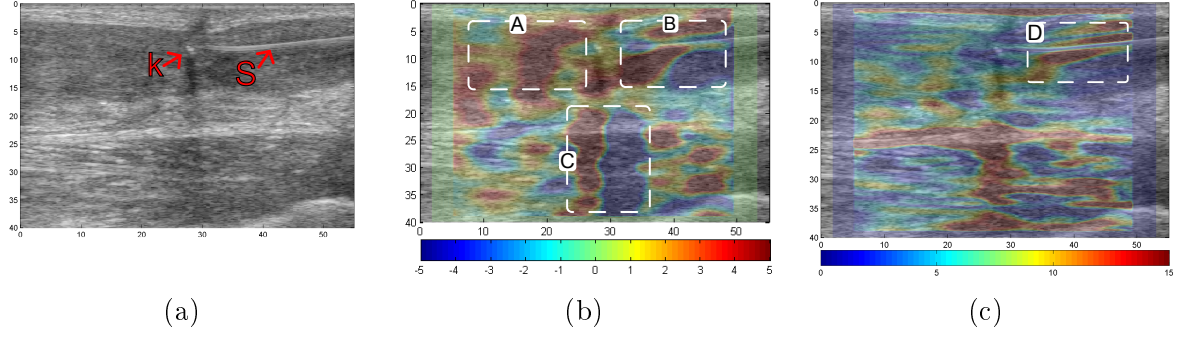


Figure 7.6: (a) B-mode image of an Achilles tendon 6 weeks post rupture that includes a long section of suture. S is a section of surgical suture, k is the knot from the suture which causes a thin shadow below it. (b) X-direction strain image (colour scale in %). ‘A’, a fairly uniform area of high strain within the tendon which could be selected as a region of interest. ‘B’, an area where the strain estimation has been affected by the presence of surgical suture. ‘C’, area of “high-low” strain artefact due to discontinuity from the shadow of the suture knot. (c) Principal strain image (colour scale in %). ‘D’, area of principal strain affected by the surgical suture.

7.3.2 Slip boundary mitigation

Selection of the ROI should aim to avoid slip boundaries. Slip boundaries have been found to be well highlighted in the principal strain images and can aid the selection of tendon tissue where it may otherwise be ambiguous. Slip boundaries can be otherwise identified [196] and either discounted from mean value calculations or highlighted to users to discourage selection.

7.4 Lateral tracking shadows

7.4.1 Shadow artefact description and examples

Shadows from the tendon rupture area or thin shadows from suture knots can cause texture changes in deeper tissue that prevent the block matching algorithm from maintaining displacement continuity over that area. Very thin shadows may not be clear from static B-mode images, would usually affect axial displacement estimates only minimally, yet can still have a significant effect on lateral elastography. It is unlikely that methods based upon the appearance or statistics of the frame-to-frame images will reduce this type of artefact [197].

The discontinuity in displacement fields causes large ‘high-to-low’ strain value artefacts in the lateral strain image (figure 7.6(b), note ‘C’). This should not adversely affect mean

strain estimations within the tendon substance unless the tendon is very large (particularly relevant for rupture cases) but will certainly affect point values of strains below the blood clot or obscuring sutures.

Poor acoustic surface contact can also affect the results of lateral strain imaging more than expected. B-mode grey-scale images can appear ‘good’ with no obvious surface shadow, yet an influence from small surface bubbles can affect the image texture within the tendon. In this data set the effect is usually small and provided that a wide area that encompasses the whole artefact is selected, the results for a given ROI mean strain value should be unaffected.

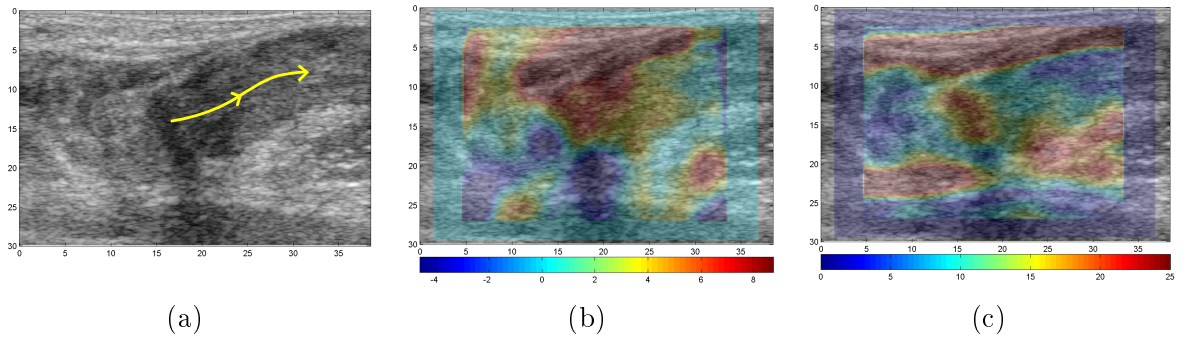


Figure 7.7: (a) B-mode image of an Achilles tendon 0 weeks post rupture where the tendon direction is clearly not parallel to the image x-axis. Arrow indicates the apparent motion direction. (b) X-direction strain image (colour scale in %). High apparent strain from non-parallel tendon boundary is indistinct from high strain at rupture zone. (c) Principal strain image (colour scale in %). High strain at centre of rupture zone is distinct from high strain at tendon boundary.

In extreme cases, shadows can cause large sections of the image to have completely incorrect displacement estimates. This, again, results in a discontinuity in the lateral displacement field. This is distinct from the previous shadow mechanism however, as there is no apparent image (caused by the signal path of superficial tissue) being tracked, the tracking algorithm is finding an entirely false local maximum to the NCC due to lack of comparable texture between frames. Figure 7.8 shows a large displacement and strain artefact due to this, but it should be noted that the tissue around the shadow has very low displacement values which may exaggerate the effect.

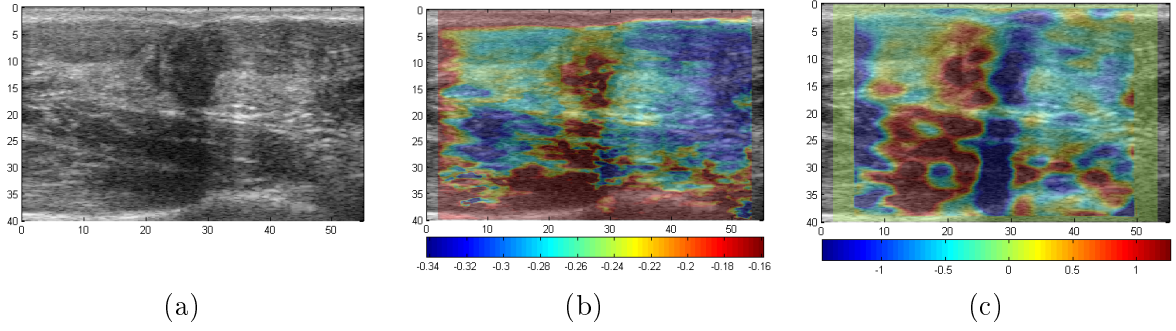


Figure 7.8: *Example of an image ultrasound Achilles tendon 1 week post rupture performing dorsiflexion motion with a large shadow region causing a decorrelation and erroneous block matching. (a) B-mode image. (b) Lateral displacement image. (c) Lateral strain image.*

7.4.2 Shadow artefact mitigation

Situations where the tracking algorithm follows the appearance of a shadow in deep texture are a fundamental problem. Shadows should not make a substantial difference to the quantitative output as long as a suitably wide region of interest is taken. Visually, they can only be mitigated by recognising that they are erroneous and disregarding or interpolating as discussed in chapter 8. For the decorrelation effects in shadow regions, it has been found that the Quality Determined Search component of the AutoQual algorithm greatly improves over multiscale approaches but in extreme cases it can still occur. The rejection of discontinuities as discussed in chapter 8 can also significantly reduce the appearance of these artefacts.

7.5 Out of plane motion

7.5.1 Out of plane motion description and examples

Out of plane motion can affect results in two distinct ways. The first is *alignment*, and primarily affects accuracy and noise in the resultant displacement images. If the ultrasound probe is held at an angle from the true angle of tensile loading of the tendon then, even if tracking is perfect, the displacement measure will be lower in proportion to the angle. 10° is likely to be the upper bounds of angle error for data acquired in the studies previously presented- data here is acquired with a 55mm width ultrasound transducer and the viable contact width of a tendon is approximately 10mm. Therefore, this pure error is likely to be small, for example, if the probe is out of true alignment by

10° then it can be expected that the strain measured is $\cos(10^\circ) \times 100 = 98.5\%$ of the true value. In reality it is likely that poor contact or textural discontinuity will be noticed by an experienced ultrasonographer before it reaches that level.

However, there is another effect that this can have: that as the tissue moves along the direction of motion, it gradually leaves and enters the field of view. This will add inaccuracy to the tracking algorithm in a less predictable way (especially when combined with distortion from compression) and will consequently add to the variation of local point estimates from the true value.

The second aspect of out of plane motion is similar to that described by discontinuous tissues, but may be less obvious in the ultrasound B-mode image. Like the discontinuous tissue type artefact, the result is a region where displacement is not continuous (figure 7.9(b)) and results in a high positive followed by high negative strain (or vice versa).

Here, continuous tissues from mechanically separate tissue can pass through the plane of motion at an oblique angle (figure 7.9(a)). These could take the form of cylindrical bodies, resulting in circular local artefacts, or from sheet-like structures from different muscles, fat or tendon sliding over each other. In the region of the Achilles tendon, the flexor hallucis longus or plantaris tendons can cause these effects as they do not always present themselves fully in the image plane as in figure 7.5(b)).

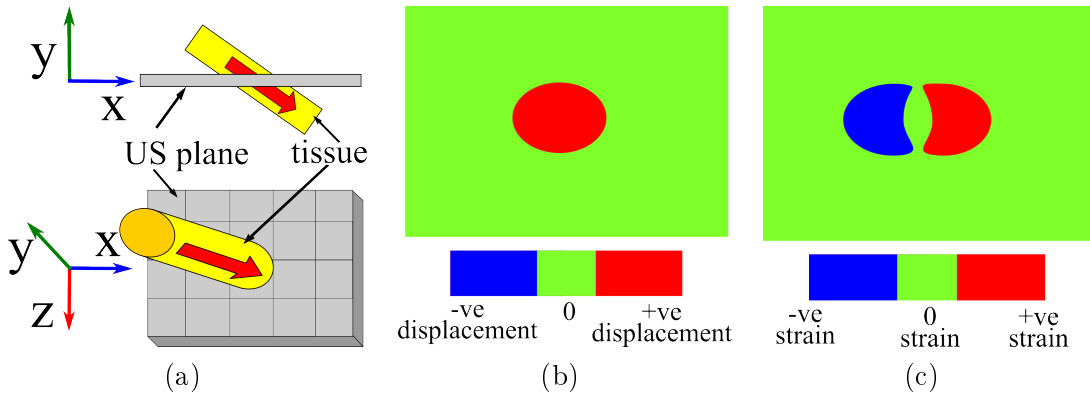


Figure 7.9: (a) Illustration of a body (yellow) moving out of the plane of the ultrasound image (grey). (b) Illustration of the resultant **displacement** image from out of plane motion of body. (c) Illustration of the resultant **strain** image from out of plane motion of body.

7.5.2 Out of plane motion mitigation

During the data acquisition stage, sonographers should try to keep the imaging plane in line with the direction of motion of the tissue structure of interest to ensure that displacement measurements are relevant. It may be possible that some sort of mechanical jig or holster for the probe would help. However, this error has been shown to be relatively small. The effect of tissues passing through the plane of motion is relatively rare, and for the measurement of Achilles tendon strains it is not assumed to affect results.

7.6 Jerky motion

7.6.1 Jerky motion description and examples

Jerky motion can occur either due to mechanical issues from performing passive motion or if the subject activates their muscles voluntarily, possibly as a result of discomfort. This can cause individual frames where the high speed of motion makes the tissue difficult to track maintaining the visual plane is difficult. This leads to a patchy appearance in the displacement image and affects the strain image (figure 7.10).

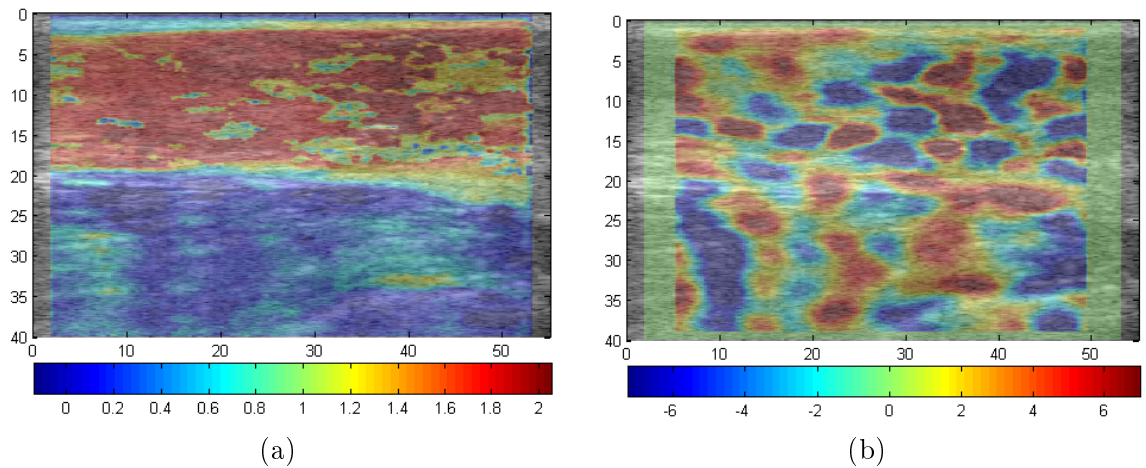


Figure 7.10: *Example of lateral elastography analysis of a subject (12 weeks post rupture) performing dorsiflexion. The flexion was not smooth as the subject twitched their foot during image acquisition. (a) Lateral displacement image (mm). Two of the sequence frames with very rapid motion contributed large areas where the block matching algorithm failed to find an acceptable match, resulting in the patchy appearance. (b) Lateral strain image (%). The patchy appearance of the displacement image has resulted in a highly confused strain image over the tendon region.*

This visual effect is not just cosmetic, as it indicates that a smooth, linear strain was not imparted. Figure 7.11 shows the mean displacement and cumulative strain values

for two sequences taken from the same subject where one exhibited jerky dorsiflexion motion and the other was smooth. In this instance, the uneven motion has contributed significantly to the value of strain measured and will

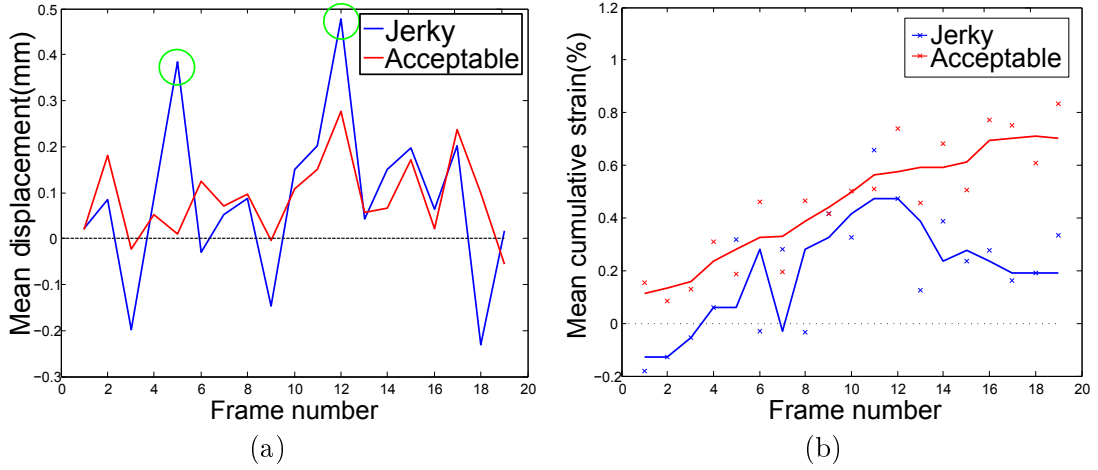


Figure 7.11: (a) Mean frame-to-frame displacement values for ROI in Achilles tendon with jerky motion and smooth motion as indicated (legend). The green circled points indicate the high displacements which coincided with frame-to-frame displacement images that has a disrupted pattern. (b) Mean frame-to-frame cumulative strain for jerky and smooth motion sequences. The strain or strain gradient are highly dependent upon where the sequence is considered to have ended with the Jerky motion, whereas the acceptable motion produced a more consistent strain gradient.

7.6.2 Jerky motion mitigation

Regularisation (such as described in chapter 8) could help with the appearance of the images, but it is unlikely that it would alter the underlying non-linear motion and thus the cumulative strain quantity would still not be comparable to acquisitions where the motion was smooth.

7.7 Chapter conclusions

This chapter has described a range of imaging artefacts found from lateral elastography of Achilles tendons and suggested strategies for minimising their effect on quantitative analysis. The simple rules are in line with good practice: ensure a smooth acquisition, avoid slip boundaries and take a wide region of interest where discontinuities are unavoidable. These artefacts highlight, however, that the resultant images from lateral elastography require an extra degree of consideration over axial elastography - the resolution and precision of the images is fundamentally lower and as such should be considered as an analysis

of a region suitable for quantitative measurements rather than for detection-type problems as is common for carcinoma detection.

Of the artefacts described, out of plane motion and local error variation are most common in healthy tissue. In cases of rupture, shadows from suture knots or from blood clot tissue are far more significant in affecting the qualitative and quantitative assessment of tendon health by lateral-motion elastography. Out of plane motion is likely to be less of an issue within the tendon substance itself, but could be of more consequence at the tissue boundaries, where slip conditions could also contribute to misleading areas of high strain. For the continued development of acceptable imaging and quantitative assessment of lateral strain in the Achilles tendon, careful protocols for motion, training about the image artefacts for assessment and development of further computer vision methods to minimise the impact of these artefacts are expected to further improve the quality of results generated.

Chapter 8

Quantitative strain measurement with smoothing and discontinuity removal

The aim of this chapter is to assess the use of regularization to improve quantitative analysis of either point or ROI mean estimated lateral strains in ruptured Achilles tendons. Specifically, it is investigated whether regularisation can be used to address some of the artefacts discussed in chapter 7.

Presented is a displacement field approximation framework using 2D bicubic smoothing splines that allows three different mechanisms of regularisation: a *weighting factor* which allows relative greater significance to be placed on displacement estimates with a higher NCC value, a *sharpness factor* that can be decreased to provide a smoother displacement field and a *reject factor* that allows individual estimation points to be ignored in the assessing of the whole displacement field. This 2D bicubic smoothing spline representation also provides simultaneous results for axial and lateral strains by assessing the spline coefficients at the nodal points.

These three regularisation parameters are varied and used to assess their effects upon artefacts typically found from lateral tracking of ultrasound image sequences of ruptured Achilles tendon, with tests using synthesized artificial data, phantom data and example *in vivo* data.

Reducing the sharpness factor was shown to decrease effects from local errors in the displacement field and can effectively remove small local discontinuities. Weight factor had minimal effect but slightly increased signal-to-noise ratios when set to high values, particularly when there are large amounts of local error variation in the displacement field. Reject factor is shown to be a potentially powerful method for removing the qualitative impact of discontinuities from shadows, and can greatly improve signal-to-noise ratio. It has a much greater effect upon mean strain values over a region of interest than sharpness

or weight factors. This can be beneficial, but runs the risk of leading to additional error particularly if large areas of the displacement impact fall outside of the reject factor criterion. Increasing the amount of regularisation from all three factors was shown to have minimal effect on the trends in lateral strains found in chapter 6, and high regularisation reduced the sensitivity to changes seen in mean strain values week-by-week.

Regularisation is shown to be a useful potential tool for improving the quality of strain images and reducing the impact of shadow and random variation strain patterns. However, caution should be used when applying aggressive regularisation strategies as they can reduce sensitivity to strain changes or, in some cases, cause additional errors.

8.1 Background

Measurement of local lateral strain from a densely sampled, unregularized displacement field is highly prone to artefacts from both noise and local discontinuities due to poor signal cohesion (chapter 7). The very premise of ultrasound elastography relies upon the appearance of tissue in one frame to be much like the appearance of the displaced and stretched (or compressed) tissue in the next frame. Unfortunately, this may not be the case, principally due to the dependence of appearance upon the whole signal path such that superficial elements can have a substantial impact on deeper tissue appearance (for example, shadows).

However, the previous work from *in vivo* and gelatine phantom experiments (see chapters 4, 6 & 7) show that that the majority of the image can be expected to comprise of good estimates of displacement. Therefore, regularization schemes could be developed that attempt to use the best regions to reinforce or replace those other regions that do not conform. Several different strategies could be taken: to smooth the displacement field by filtering (2D frequency filtering, Gaussian filtering, median filtering or wavelet denoising etc.), regularization based upon geometric factors like curvature of shapes [198], explicit modelling (such as finite element analysis) or image analysis to ascribe greater importance to some estimates than others.

The problem of noise and discontinuities are exaggerated for lateral elastography. Lateral block matching and strain image estimation techniques are currently limited to

research rather than embedded in commercial systems. Lateral displacement estimations are inherently less accurate than axial strains due to lower spatial resolution, lack of signal continuity in the lateral direction, path dependence of texture (for deeper tissue), additional mechanical complexity causing slip/shear at tissue boundaries and out of plane motion. These can lead to potentially large artefacts in resulting strain estimation images, which can significantly affect local-point quantitative measures of strain as well as the qualitative impact of the strain image. For example, it is easy to mistake a local positive-to-negative strain image artefact (from a discontinuity in the displacement field) as a local high strain if the image colour limits are set to ignore negative strain.

The previously described Window method (chapter 4) took small windows (approx $2\text{mm} \times 2\text{mm}$) of the displacement field and used a linear fit of the displacement weighted by the normalised cross correlation (NCC) coefficient in order to estimate the gradient in each direction. The end effect, however, has little clear advantage over the Difference method ¹ with a blurred displacement field and presents locally smooth strain fields but with little compensation for discontinuities. NCC values tend to be fairly consistent within the Achilles tendon (>90% NCC is not unusual from the *in vivo* experience with Achilles tendon rupture cases) and many of the discontinuities that cause problems are only weakly differentiated by the NCC. For example, a very thin shadow can have similar appearance in one frame to the next, so the block matching algorithm will return a low displacement which is discontinuous to surrounding tissue but with a high NCC. This type of artefact is typical for poor surface contact or from knots in surgical suture (figure 8.1). Similar shadows can also be caused from poor contact at the skin surface due to small air bubbles in the acoustic coupling gel. Larger, more obvious shadows are also not uncommon, especially in areas with large haematoma in early weeks since rupture (figure 8.1(c)).

¹Difference method previously described as the difference displacement image between pixels divided by the pixel spacing

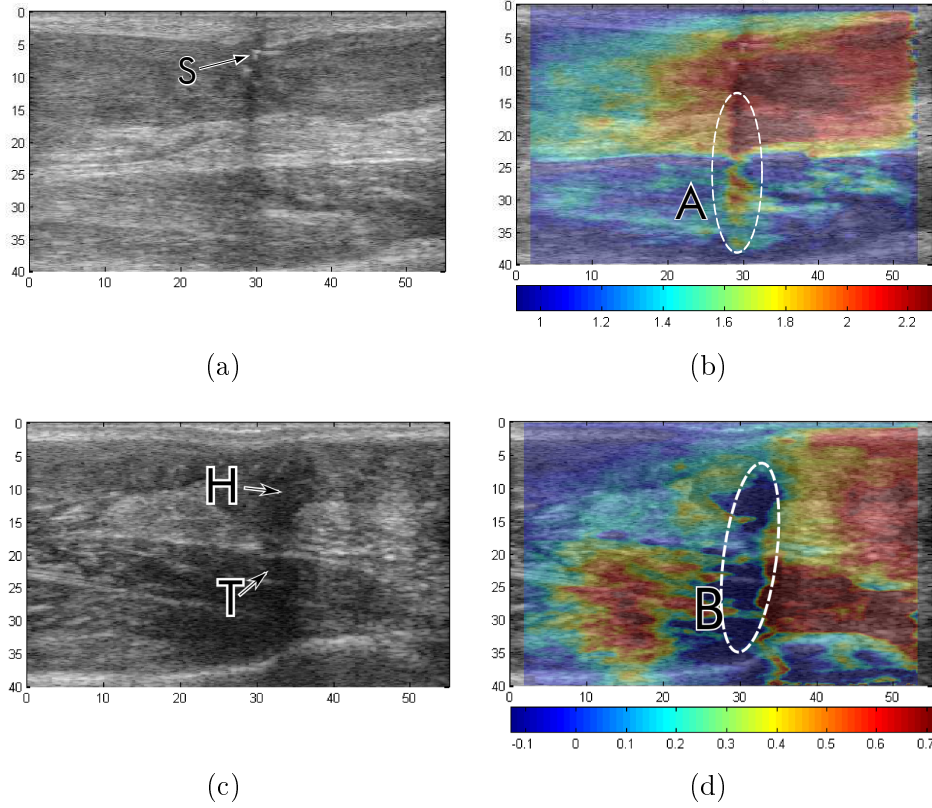


Figure 8.1: (a) Example B-mode image of Achilles tendon 6 weeks post rupture. *S* shows the position of a suture knot which causes a thin shadow in deeper tissue, but which is not immediately obvious. (b) 2D lateral displacement field (mm) of Achilles tendon during controlled dorsiflexion. The suture knot has moved relative to the deeper tissue and the shadow has been tracked causing a discontinuity in the displacement field, *A*. (c) Example B-mode image of Achilles tendon 0 weeks post rupture. *H* shows a large dark area caused by blood clot, *T* shows the resultant shadow region. (d) 2D lateral displacement field (mm). The block matching algorithm has failed to find a good match due to the haematoma and shadow, resulting in a discontinuity and low displacement *B*.

8.2 Methods

Using knowledge of spline formulation from earlier chapters, presented here is an approximating 2D smoothing spline regularization method that is computationally faster than the Window method, allows for the similar weighting and smoothing effects upon the strain field generated and additionally allows data points to be excluded if they fall outside of certain selection criteria. This is used, in this chapter, as an initial framework to investigate the quantitative and qualitative effects of regularization of the strain field and determine if they can have beneficial or detrimental effects for synthesized, phantom experiment and *in vivo* examples.

8.2.1 2D Smoothing splines to estimate strain

Splines are piecewise functions used to approximate more complex ones. If a bicubic polynomial function is used (as previously described, chapter 4 equation 4.2, repeated here) and nodal points are taken at a regular grid spacing equal to the pixel locations, then the value of the x and z derivatives at the nodal points ($x=0, z=0$) in each location will be equal to the ${}_1k_{i,j}$ and ${}_2k_{i,j}$ coefficients respectively.

$$f_{i,j}(x, z) = \sum_{p=0}^3 \sum_{q=0}^3 {}_qk x^p z^q \quad (8.1)$$

where $0 \leq x \leq 1, 0 \leq z \leq 1$

When applied to the axial and lateral displacement fields this provides values for the axial, lateral and shear strains. These derivatives can also be used to determine the shear strain, maximum shear strain and principal strain as previously described.

The method described by Viola et al. for 2D bicubic spline generation [144] is convenient, as any type of 1D spline can contribute to its formulation. This has already been described for RF signal approximation by allowing or disallowing overshoots in the splines (chapter 4). Smoothing splines are n th order piece wise polynomial functions but without the requirement to pass through the defining points exactly. As such they are considered as *approximation* splines rather than *interpolation* splines. They are generated by minimising an energy function E of spline s according to a sharpness parameter (S_f) and point weightings (w_i) while still meeting the boundary conditions of a continuous second derivative:

$$E = S_f \sum_i w_i^{W_f} (y_i - s(x_i))^2 + (1 - S_f) \int \left(\frac{d^2 s}{dx^2} \right)^2 dx \quad (8.2)$$

where y_i is the displacement value found at point i by a block matching mechanism.

This allows both an amount of arbitrary smoothing in the strain field and the use of weighting according to the confidence in the results received. As previously mentioned, the NCC alone only weakly differentiates, so an additional weight factor parameter W_f is included to improve the differentiation between importance of strain values. W_f has been set as a power factor to allow us to non-linearly affect the influence, and is defined

for NCC between 0 and 1. 1D smoothing splines have previously been used in the field of elastography in order to smooth noisy displacement fields from 2D elastography [133]. A smaller sharpness factor results in less adherence to points and a smoother field. As such it should be noted that smoothing splines are *approximating* splines rather than interpolating splines.

Using smoothing splines should have the effect of reducing the effect of small, local discontinuities and noise and so provides a smoother strain estimation field. Thus this acts as a form of local regularization.

Finally, this method can accommodate irregular data point sampling in order to ignore poor estimates according to a given rejection criterion. If correctly selected, discontinuities can be completely ignored by the spline generation process, therefore minimising the effect of larger discontinuities such as shadow artefacts. Approximations of displacement values over the ignored region can then be re-evaluated at the pixel positions by evaluating the spline function.

The rejection criterion defined here is to reject a data point if more than R_f times the standard deviation of the existing data points to a linear fit to the displacement (figure 8.2). Note that this definition means that *smaller* R_f values lead to greater amounts of rejected points and smoother resultant strain fields.

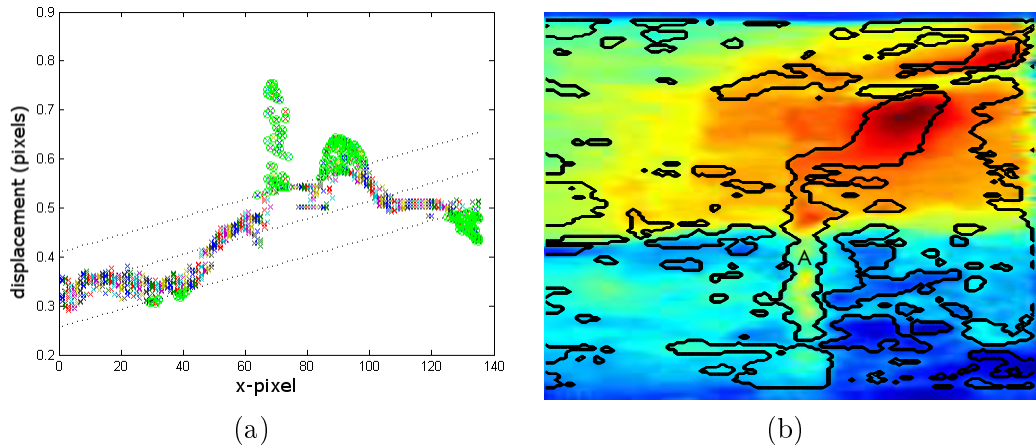


Figure 8.2: (a) Example of a linear fit to a series of lateral displacement points in the x -direction with points outside the reject factor ($R_f=1$) $\times$ standard deviation highlighted. Displacement data shown is 9 horizontal lines from a 2D block matching analysis of an Achilles tendon 6 weeks post rupture. (b) 2D lateral displacement field from *in vivo* Achilles tendon example with rejected regions shown by black-line enclosed regions. ‘A’; shows a discontinuity region caused by a suture knot in the tendon.

This framework allows the investigation of these three governing factors: sharpness factor (S_f), weight factor (W_f) and reject factor (R_f) in order to assess if there is a significant impact to quantitative results from the resultant strain estimation image. Note that this definition means that *smaller* R_f values lead to greater amounts of rejected points and smoother resultant strain fields.

In this implementation the smoothing splines are applied to each frame of the sequence in order to minimise egregious errors at their source. The frame-by-frame displacements are then summed and a final bicubic is calculated without further regularization ($W_f = 0$, $R_f = \infty$, $S_f = 1$) in order to obtain the derivative values for strain. Although this could be performed as a single step on the final summed frame, this method has been developed for subsequent use to help determine frame-by-frame strains.

The resultant strain images encompass the same region as the displacement field (the Window method requires a border region), are computationally faster to generate than with the Window method and yet can be used to approximate similar levels of smoothing (figure 8.3(b)). It is assumed that this method is valid for the conclusions reached from previous chapters.

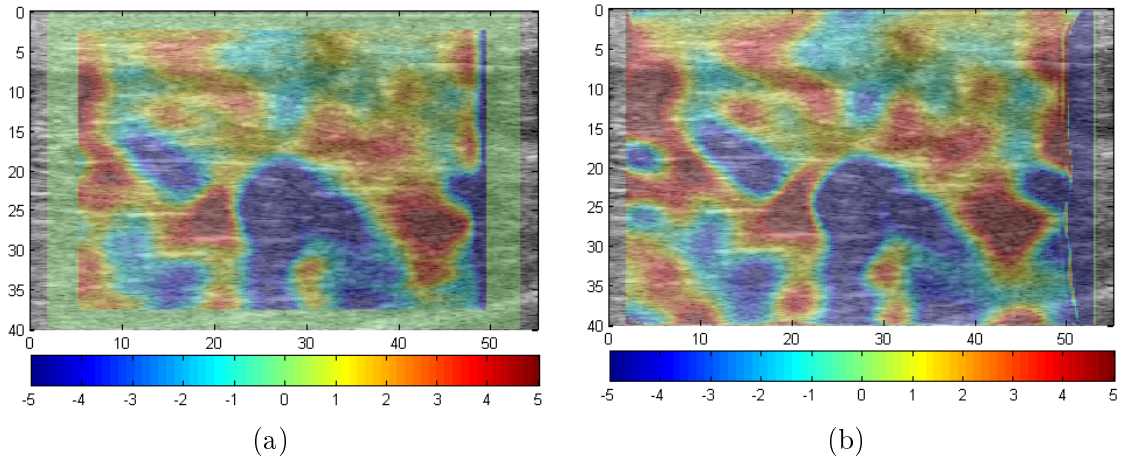


Figure 8.3: (a) Example of lateral strain estimation image evaluated by the ‘window’ method. (b) Example of lateral strain estimation image evaluated by the ‘smoothing spline’ method with no reject factor or weighing factor applied. The smoothing factor can be set in such a way as to approximate the output from the window method but with a wider field of view.

Test	Data type	Tension speed (% strain per frame)	Added artefact (% of image width)	Added Noise (% max. displacement)
A	Synthesized	1px/frame (0.37)	No	1 - 11%
B	Synthesized	1px/frame (0.37)	2-20%	5%
C	Phantom	4.0mm/s (0.35)	-	-
D	Phantom	0.5 - 5mm/s (0.04-0.44)	-	-
E	<i>In vivo</i>	-	-	-

Table 8.1: Description of test data used to assess performance of smoothing spline regularization.

8.2.2 Data and tests

In order to assess the properties of the different regularization factors in the 2D bicubic smoothing spline method, a series of experiments were conducted using synthesized displacement fields, displacement fields from phantom block compression experiments, and *in vivo* data from subjects with ruptured tendons performing controlled dorsiflexion (DF).

All tests are summarised for reference in table 8.1. For comparative purposes they are measured by the absolute error of mean strain to ground truth strain (for phantom and synthetic data only) and by image signal-to-noise ratio (iSNR - equation 8.3) over a selected region of interest (ROI). The mean value error describes any dynamic effect of the methods on the quantitative outcome and the iSNR describes the sensitivity of the output to ROI selection.

$$iSNR = \frac{\mu_{\varepsilon}}{\sigma_{\varepsilon}} \quad (8.3)$$

where μ_{ε} is the mean strain and σ_{ε} is the standard deviation over the ROI.

All displacement data from phantom and *in vivo* experiments are found using the Autoqual block matching algorithm as previously described (chapter 4).

Test A: Assessment of a synthesized lateral displacement field with a constant linear gradient from 0 to 1 pixel per frame and a sequence of 19 frames (a similar length to

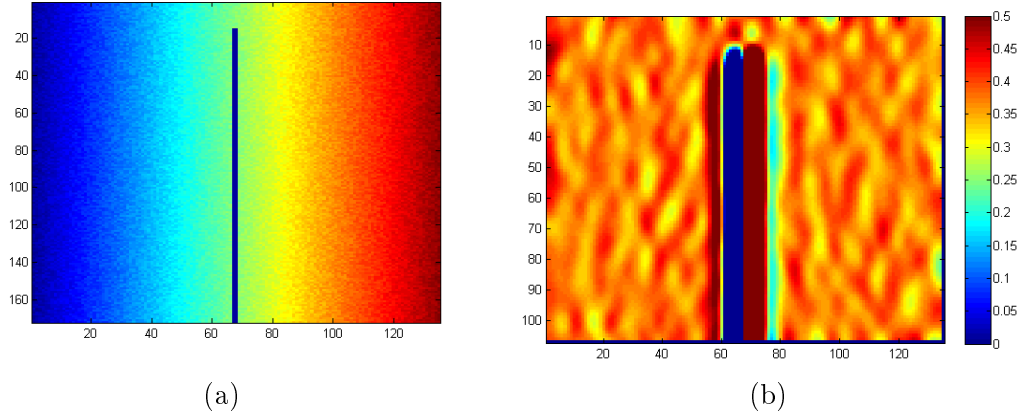


Figure 8.4: (a) Example of synthesized displacement field (0-1 pixels) and shadow artefact with zero displacement. (b) Example of strain (%) estimation field derived from (a) with large high-to-low artefact caused by the shadow.

sequences used for *in vivo* examples). Random (even distribution) noise is applied to each frame at amplitude, A , at 1%-11% value of the maximum displacement experienced by using the Matlab function $A \times ('rand' - 0.5)$. Even distribution represents a worst case scenario to test the capability of smoothing the field by adjusting the sharpness factor (S_f) and of the reject factor (R_f).

Test B: Assessment of a synthesized lateral displacement field as per test A. Random noise is added to each frame at an amplitude of 5% of the maximum displacement. Simulated shadow artefacts were included as shown in figure 8.4. Shadow artefacts were represented as a single thin, vertically aligned area of zero displacement with various widths (2-20% width of total displacement field). This test is to prove the capabilities of the reject factor and the sharpness factor to compensate for a shadow discontinuity, assuming that it does not cause a difference in the NCC. The test is repeated for 20 different random noises (with the same amplitude) for each of various widths of artefact up to 20% of the width of the image (27 displacement image pixels wide). Reject factor was set at 1 standard deviation and sharpness factors of 0.1 to 0.5.

Test C: Assessment of phantom data with no added shadow artefact to investigate if the weight factor impacts on the quantitative results with good signal strength. This phantom data was the same as used in chapter 4 and is a 3.5mm compression of a 80mm sided cube of gelatine at 2.5mm/s grip to grip speed. Phantom displacement data provides a known strain as a ground truth for comparative purposes but also includes a valid NCC

Scenario	R_f	S_f	W_f
Repair 1	1	0.9	4
Repair 2	0.6	0.75	10
Repair 3	0.4	0.4	10

Table 8.2: *Parameters used for in vivo experiments with 2D bicubic spline regularization.*

factor to assess the impact of weight factor (W_f) in areas of good signal strength.

Test D: Phantom data from compression at different grip-to-grip speeds to test if the reject factor (R_f) affects the mean error and image SNR. The data for this is the same as used in section 5.4, and was conducted for grip-to-grip speeds of 1 to 5mm/s.

Test E: Testing on *in vivo* data from post rupture Achilles tendons to observe the effect on existing artefacts, on strain mean values and image SNR.

2D bicubic smoothing splines were used to estimate strains from displacement fields for all DF motion captures previously described for 21 subjects with Achilles tendon rupture up to 24 weeks (the data set from chapter 6). Three different scenarios were enacted with parameters described in table 8.2. These scenarios are intended to show a minimal regularization, a moderate regularization and a heavy regularization. These were compared against the original ‘window’ method.

8.3 Results

8.3.1 Test A: Synthesized strain, various noise

The sharpness factor had a substantial effect on the image SNR. Displacement fields which had low amplitude noise had much greater iSNR values with lower sharpness factor, but tended toward the same (<1) SNR values as for higher values of noise (figure 8.5(a)). Mean values were only minimally affected with a range of differences observed of 0.01% strain and were most similar when the sharpness factor was high (figure 8.5(b)).

NCC Weight factor (W_f) had the smallest influence, allowing extra smoothing for higher factors which led to higher SNR values (figure 8.6(a)), but having negligible effect on the mean value of strain measured (figure 8.6(b)).

Reject factor had a large effect on the SNR values with lower R_f causing a smoother strain field to be developed (figure 8.7(a)). Mean values of strain were affected by neg-

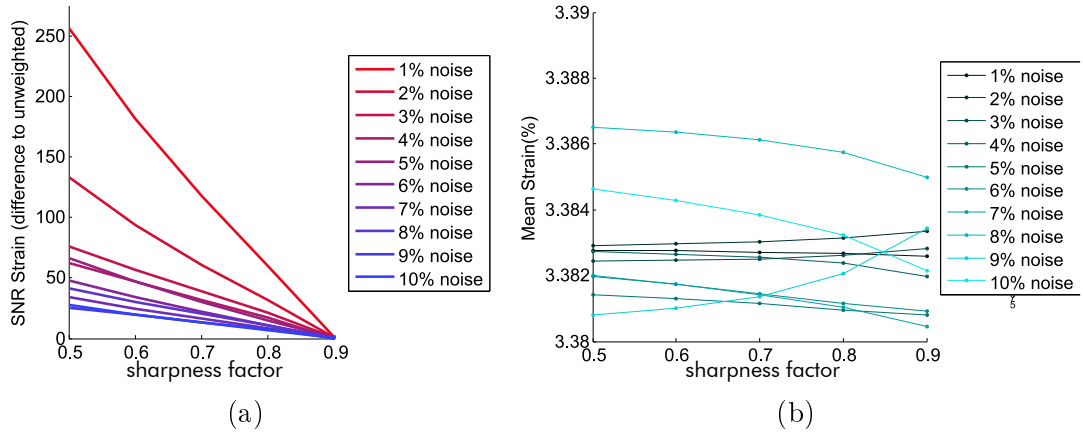


Figure 8.5: (a) The difference between *sharpness* factor adjusted and reference strain image SNR values for a linear synthesized displacement field with different amplitudes of added random noise. (b) Mean values of strain found in the ROI for a linear synthesized displacement field with different amplitudes of added random noise and different *sharpness* factors.

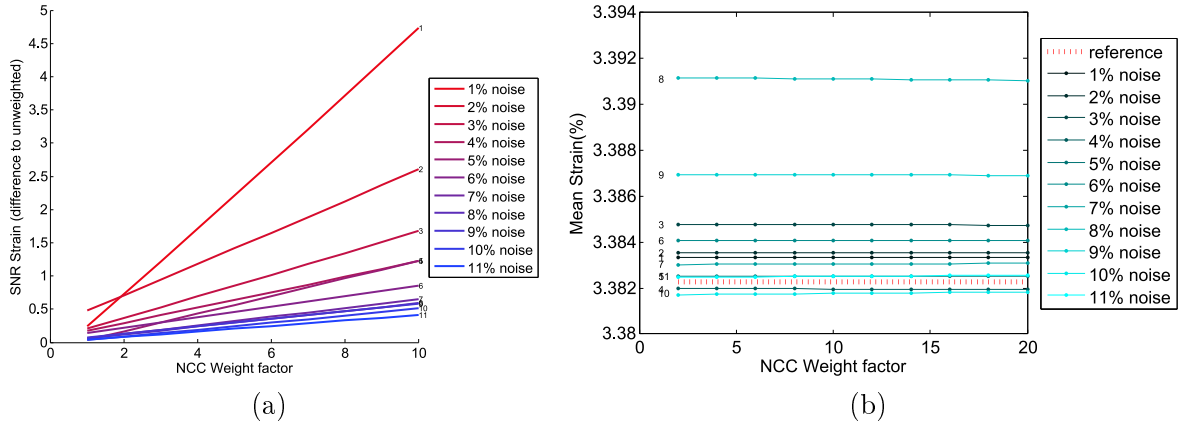


Figure 8.6: (a) The difference between *weight* factor adjusted and reference ($W_f = 1$) strain image SNR values for a linear synthesized displacement field with different amplitudes of added random noise. (b) Mean values of strain found in the ROI for a linear synthesized displacement field with different amplitudes of added random noise and different *weight* factors.

ligible amounts (with a range of approximately 0.01% strain) and with no clear trend relating to noise amount or sharpness factor (figure 8.7(b)).

8.3.2 Test B: Synthesized strain with shadow artefacts

Added artefacts were removed effectively from synthesized linear displacement fields by use of the reject factor. Artefacts of all widths were visually removed from the strain and displacement fields. The interpolated area appeared uniform, although with some small variation which was allowed for by the bicubic function - however, this ensured that fields are locally smooth. The removal of the artefact substantially improved iSNR values

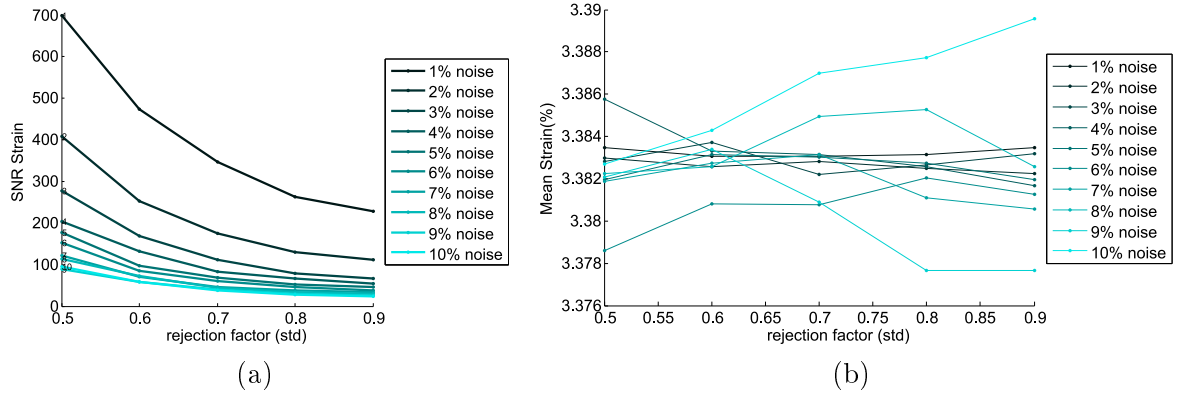


Figure 8.7: (a) Strain image SNR found over the ROI for linear synthesized displacement field with different amplitudes of added random noise and different **reject** factors (b) Mean values of strain found in the ROI for a linear synthesized displacement field with different amplitudes of added random noise and different **reject** factors.

to similar values of those in the original (reference) strain found with no added artefact (figure 8.8(a)). The random noise caused a small variation in both iSNR value and mean strain value over successive analyses for the ROI. The range of mean values found was similar to those found in test A (figure 8.8(b)).

Sharpness factor was less capable of visually removing the artefacts when the displacement and strain fields were reviewed. Only when very small artefacts and very low values of sharpness factor ($S_f < 0.3$) are used do the artefacts visibly disappear and a substantial improvement in SNR is achieved.

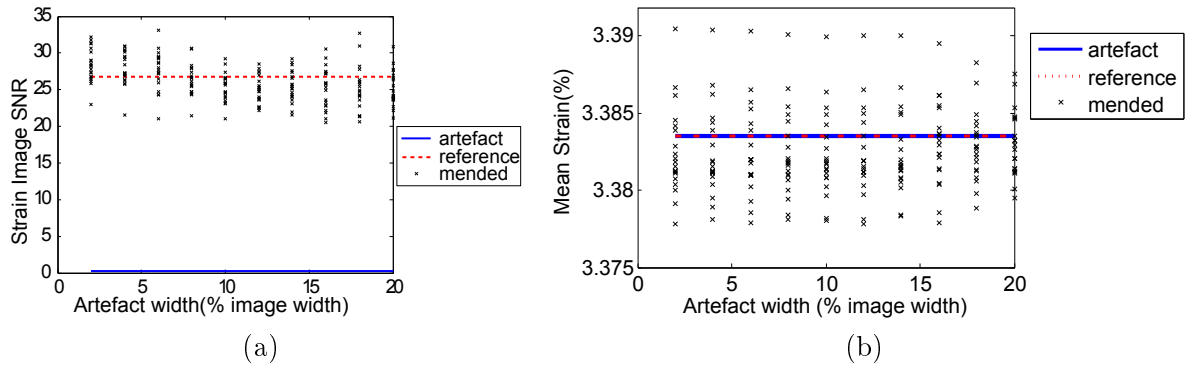


Figure 8.8: (a) Strain image SNR over the ROI for different widths of artefact (% image width) and (b) Image mean strain values over the ROI for different widths of artefact (% image width) on synthesized linear displacement fields with 5% amplitude noise. 'Mended' results found with $W_f = 0$, $R_f = 1$ and $S_f = 0.9$.

8.3.3 Test C: Phantom data, various weight factors

Phantom data showed that the weight factor did have an impact on mean values and SNR values compared to the reference (no weight factor, but the same sharpness factor, figure 8.9). This impact is, however, small, influencing up to 0.012 SNR (-38.4dB) and up to $4 \times 10^{-3}\%$ which is negligible. Results indicated that the influence of the weight factor is dependent on the sharpness factor, and it should be noted that if the sharpness factor is 1 the weight factor will be defunct and not effect results.

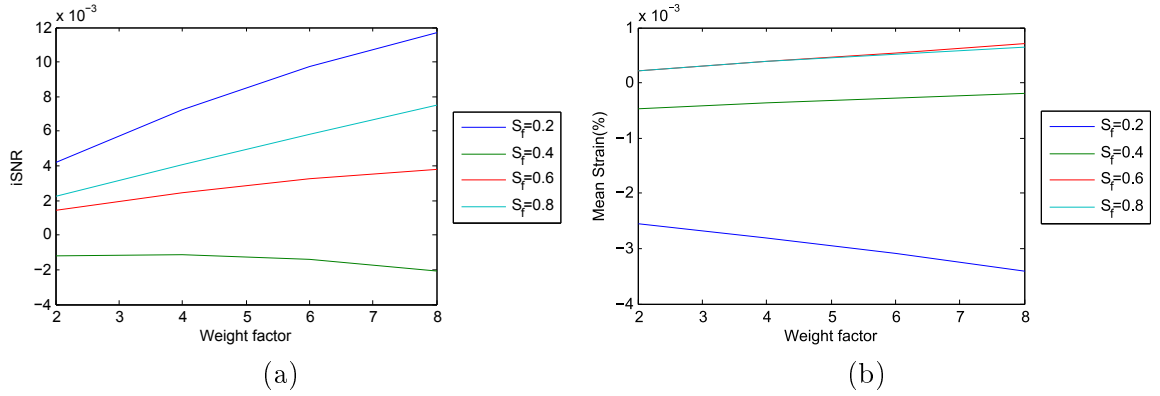


Figure 8.9: (a) Difference between strains found with different weight factors and reference strain image SNR. (b) Difference between strains found with different weight factors and reference mean strain values. Tests were from 80mm sided phantom block decompressed by 3.5mm at a speed of 4.0mm/s.

8.3.4 Test D: Phantom data, various speeds, various reject factors

Tests using the reject factor on phantom data had a similar effect on the SNR to those seen on synthesized data (Test A). However, the reject factor had a more dramatic effect on mean value especially for the faster phantom compression experiments with higher noise levels. This, especially for the smallest reject factors, led to very high strains being measured with large deviation to the target strain (figure 8.10). Changes to the weight factor and the sharpness factor had negligible impact on the mean strain value and affected the signal-to-noise ratio in a similar manner to that described by Test A.

Compression speeds up to 3mm/s showed very little difference in mean value for different values of the reject factor. At faster speeds the local variation in the displacement field greatly increased and larger sections were consequently disregarded by tight reject factors. Spline approximations therefore, did not have sufficient support - effectively they

extrapolated over large regions rather than approximating or interpolating around known values (see figure 8.11).

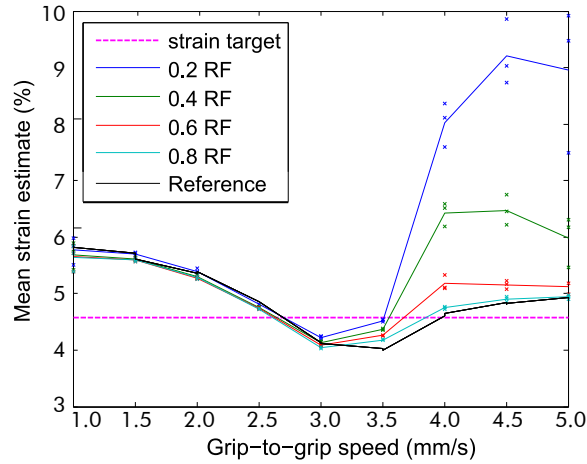


Figure 8.10: Mean strain values found from 3.5mm compression of phantom block at compression speeds of 1-5mm/s regularized with various reject factors (see legend).

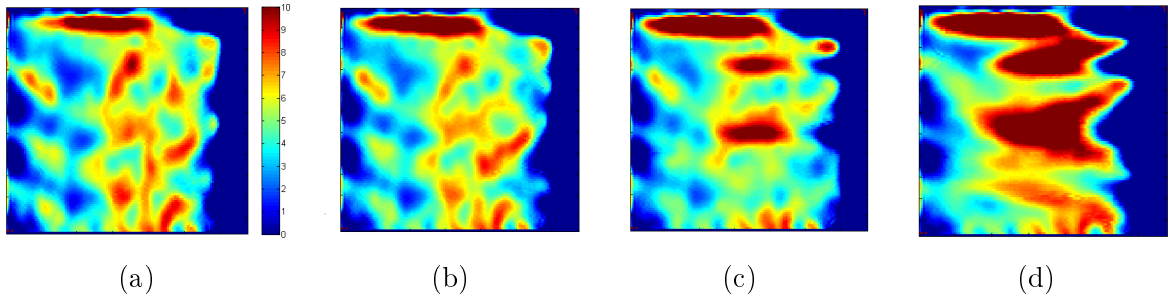


Figure 8.11: Examples of 2D strain fields obtained from phantom block compression experiments with grip-to-grip speed of 5mm/s. Different reject factors applied for regularization: (a) $R_f = 0.8$; (b) $R_f = 0.6$; (c) $R_f = 0.4$; (d) $R_f = 0.2$

8.3.5 Test E: *in vivo* tests

Tests on *in vivo* data showed some visible improvement in areas of discontinuity. This improvement increased with smaller sharpness factor and reject factor. Although the rejected points showed appeared to coincide well with the discontinuities (as in figure 8.2(b)), the artefacts seen in the strain field are not entirely removed for the values used unless the most extreme regularization is applied (figure 8.12). Displacement fields appeared much smoother, which could imply a loss of resolution, although the prevalence of artefacts in the lateral strain field could imply that it is strongly affected by noise.

When applied to the whole rupture patient data set for DF motion, strain image SNR increased predictably with a greater amount of regularization, although never approached

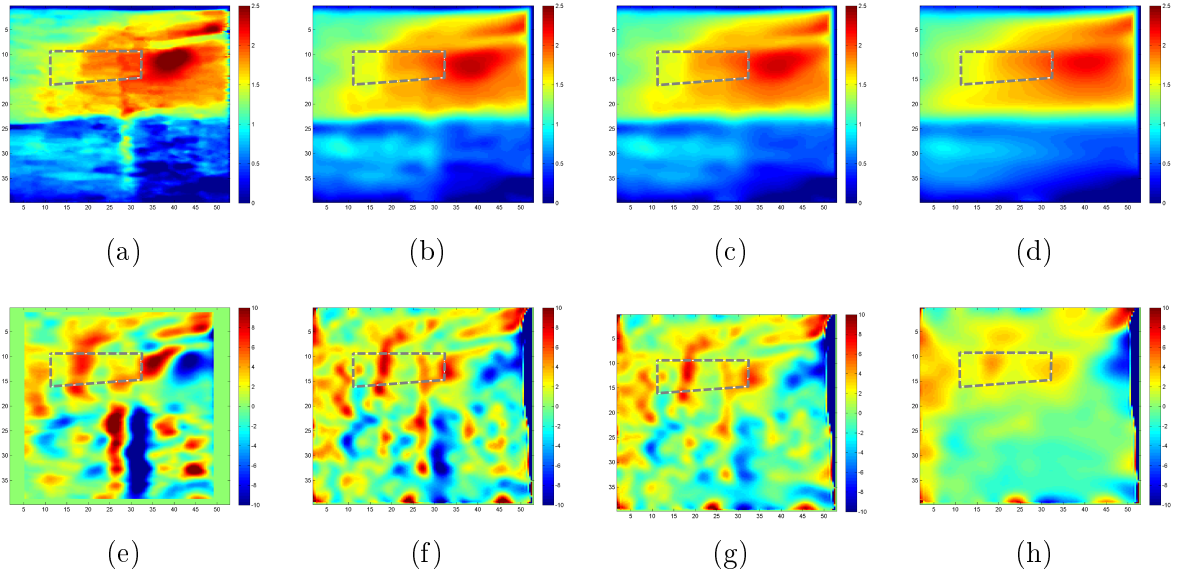


Figure 8.12: *Lateral displacement field (mm) and strain (%) images of example dorsiflexion motion from subjects Achilles tendon 6 weeks post-rupture. Dashed line indicates ROI. (a) & (e) Reference motion and strain images; (b) & (f) Motion and strain images regularized with ‘Repair 1’ parameters; (c) & (g) Motion and strain images regularized with ‘Repair 2’ parameters (d) & (h) Motion and strain images regularized with ‘Repair 3’ parameters*

the levels seen in Tests A-D (figure 8.13(a)). Mean strain values were significantly affected by more regularization: ‘Repair 1’ parameters had almost zero effect on the mean strain values compared to the ‘window’ method strain values. Higher levels of regularization had a greater effect, particularly in early weeks since rupture when strain values are the highest, and generally acted to lower the mean strain estimated (figure 8.13(b)). This was particularly noted for the ‘Repair 3’ parameters, where lateral strain was affected to up to -3% strain. In this worst case example there was, however, an extremely large discontinuity due to a large shadow from the rupture zone and the result from the ‘repair 3’ parameters did provide a more intuitively understandable strain field, with a broad, high strain field in the tendon region at the top of the image and low or negative strain in the deeper tissue (figure 8.14).

Both principal and lateral strains had lower mean values in early weeks for more highly regularized strain estimation fields (figure 8.15). Increased regularization also had the effect of reducing the spread of results in weeks 0-3, thus increasing the coefficient of variance (CoV) slightly, and had less effect on the groups spread in later weeks. Spearman correlation coefficients of regularized mean strain vs. time remained similar to the Window

method for lateral strain, but were more significantly affected for principal strain trends, with correlation coefficients reducing from 0.66 to 0.62 (figure 8.16(a)). Week-to-week distinctiveness was also affected, and Welch t-test comparisons of the week-groups resulted in higher P-values than those found in chapter 6 (figure 8.16(b)). Principal strain values were strongly affected, but differences were not substantial for lateral strain with any of the regularization strategies used.

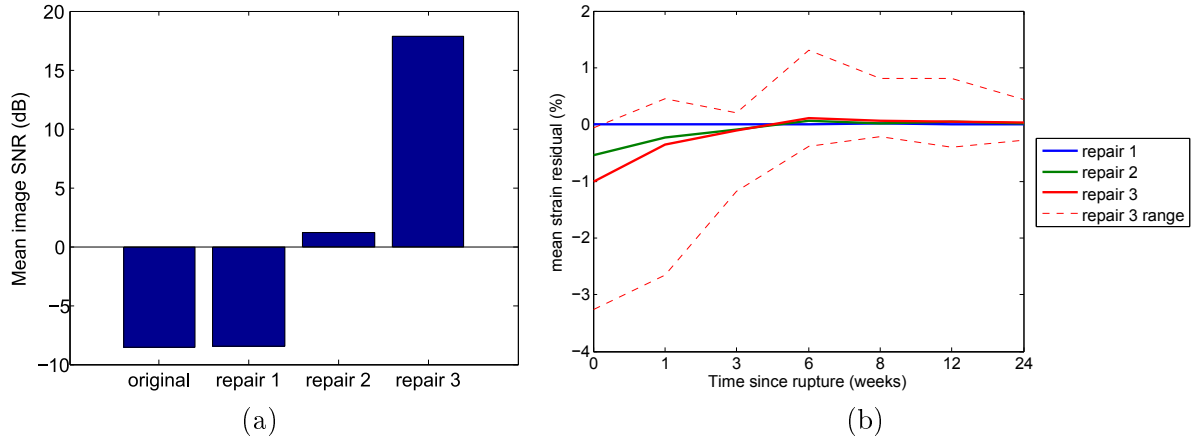


Figure 8.13: (a) Mean strain image SNR (dB) for DF motion dataset with original, and increasing levels of repair with smoothing and reject factors (repairs 1-3) (b) Residual of repaired strain images compared with original (% strain). Results are from all DF motions from 21 patients suffering from Achilles tendon rupture over 24 weeks.

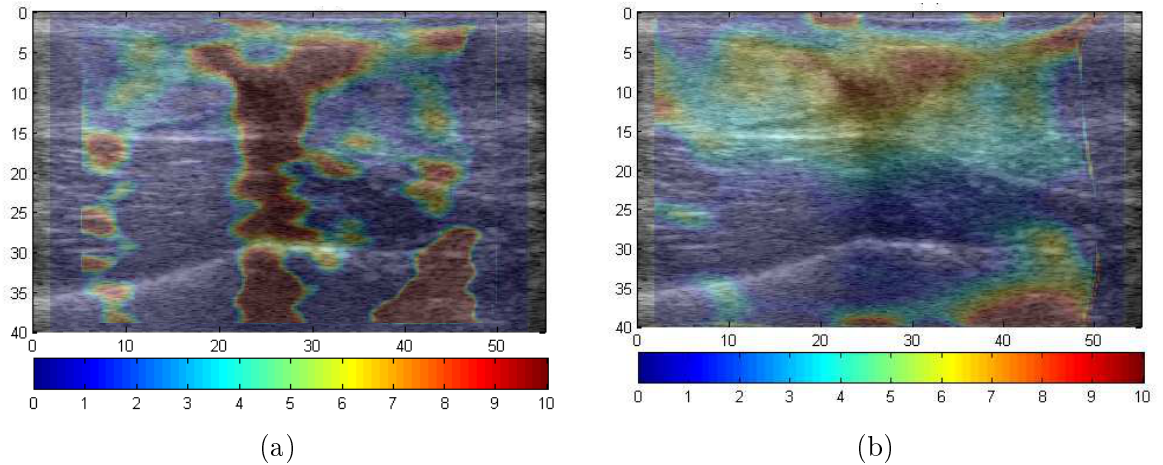


Figure 8.14: (a) Lateral strain image (%) of Achilles tendon rupture patient with large shadow artefact from DF motion. (b) Lateral strain image (%) of patient repaired with bicubic smoothing spline with 'Repair 3' parameters.

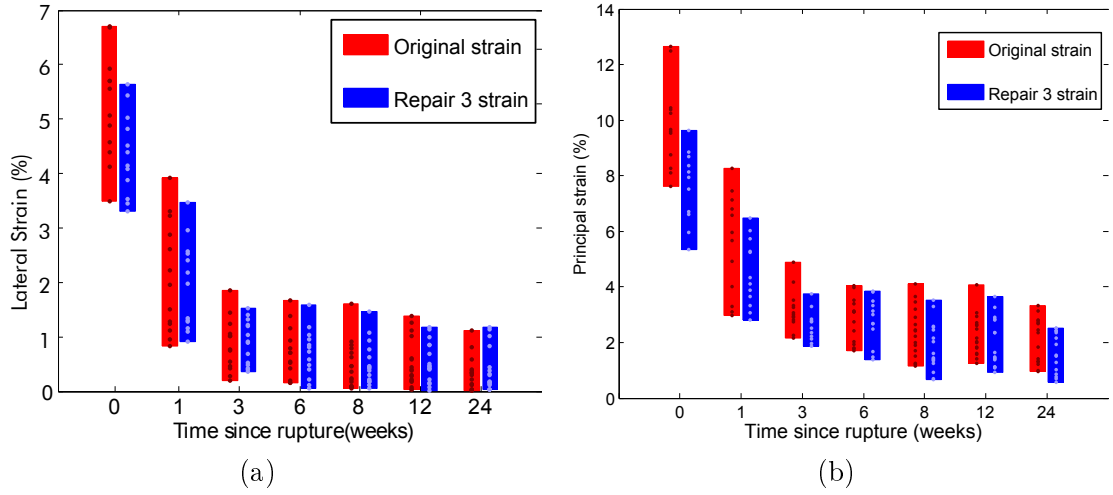


Figure 8.15: Strain values found for all patients up to 21 weeks since rupture for Unregularized and ‘Repair 3’ parameter regularization (outliers removed) (a) Lateral strain (%), (b) Principal strain (%).

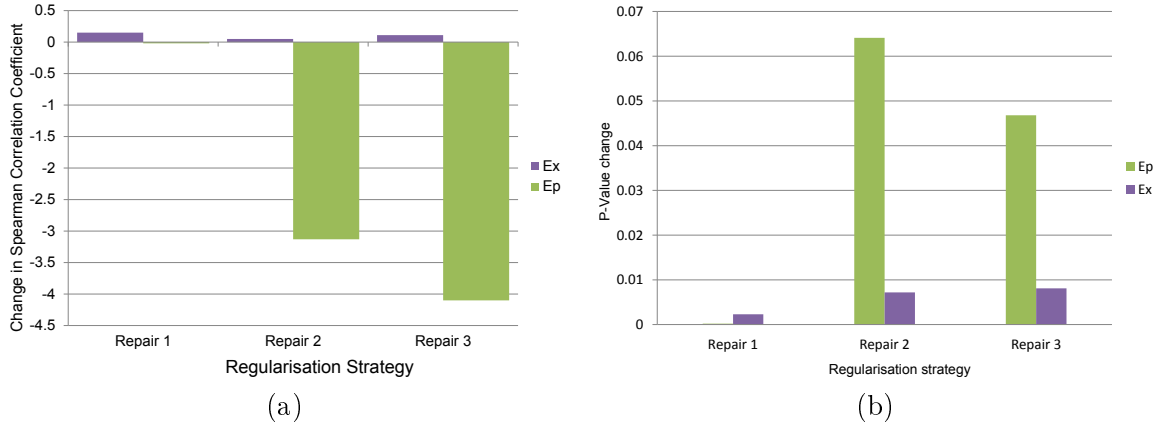


Figure 8.16: (a) Change in Spearman correlation against time since rupture for lateral (Ex) and principal (Ep) strains over data set of patients performing DF motion and for different image strain regularization strategies. (b) Change in mean p-values comparing the week-to-week strains with Welch’s t-test since rupture for lateral (Ex) and principal (Ep) strains over data set of patients performing DF motion and for different image strain regularization strategies.

8.4 Discussion

The presented method of reject uses two concepts: first, to locally smooth the displacement field in a way that it more greatly weights points with good NCC values (controlled by sharpness factor and weight factor) and second, to reduce larger discontinuities that lie outside of a specified range close to a linear fit. These constitute a form of weak modelling—only a small amount of extra information is assumed and can leave the majority of the image unaffected so that the local complexities of the strain field can be observed. As the reject factor is a threshold on included results, those results deemed to not be outside of

the rejection criterion should not be greatly affected and thus should provide the same contribution to mean strain quantities over a selected region of interest. By contrast, a more strict approach could be to fit an n^{th} order polynomial (or other function) and treat that as the explicit displacement value and not to allow for local variation [168]. The extreme extension of this is full finite element analysis (FEA) modelling based upon the 2D displacements originally calculated. This would rely upon assumptions of the mechanical properties and additional spatial information which would include additional prior knowledge into the regularization.

This study, with a variable amount of regularization under a relatively simple model, has highlighted some potential benefits and some risks of smoothing and outlier rejection. A small amount of regularization clearly does not overly impact on the quantitative aspect of the strain image: mean strain values have been shown to be preserved while image signal-to-noise ratios increase, and the detail of the strain image is not significantly lost. However, if the threshold for reject factor is lowered, the displacement field can become over-regularized and greatly distort the strain values. On the *in vivo* examples this effect was generally to lower the strain and can be seen to visually improve the distinctly different strains in different tendon regions and reduce the effect of discontinuities from shadows. However, this effect has been shown with the phantom data experiments to be capable of distorting the strain values to being far away from the real target strain.

The use of more aggressive regularization upon a large number of *in vivo* examples did affect mean strain values and the strength of both the Spearman correlation coefficients and the distinctiveness of tendon strains experienced comparing group values found at different weeks. It has been shown that mean strain values can decrease with more regularisation and this may contribute to successive weeks appearing to be more similar. It is also possible that the erroneous strain values caused by artefacts were themselves part of the distinctiveness: in early weeks artefacts are more common and larger, and decrease over time. By removing these more accurate strain values for the tissue may be estimated and yet still be decreasing the perceived capability of strain as an output metric to capture tissue property changes.

The sharpness factor had less effect on mean strain values. Also, it could not regularize

out large discontinuities seen from some shadow artefacts, seen from synthetic data experiments. If a less dense displacement field were used as nodal points for the splines then it is possible that smoothing could remove these artefacts but this would further decrease resolution of the resultant strain estimation field. The energy term in the smoothing spline formulation is similar to that found for thin plate spline or smoothing terms in isotropic filters [199] and so it may be that these methods behave somewhat similarly.

The existing framework for regularization of the noisy displacement field is potentially of further interest, and further work could be carried out to couple the x and z displacement field requirements, to include temporal information as part of the regularization which may influence or be capable of analysis of viscous elements of the strains imparted [200]. Reject factors could be further tailored to this specific problem, possibly by dilating the selection region (figure 8.2(b)). This would allow the regions surrounding known large discontinuities to be further discounted, while still allowing small discontinuities in local regions and thus not over-regularizing in those areas. Additional work could also be conducted to better define the poor data points as dismissing points by the reject factor based on a linear fit may be a crude tool. Karamalis et al. have attempted to define shadows by random walk methods, and it is possible that these could be incorporated into the reject factor criteria [201]. However, a reject factor based on an arbitrary threshold of the NCC value has been tried (which has been suggested by publications [171]). Unfortunately cases were found where NCC was high, but discontinuities were present and cases where NCC was low but displacement fields were continuous. The NCC map is highly dependent upon the speed of motion, the signal strength of the relevant tissue and the size of matching block used for displacement tracking². Setting the arbitrary threshold is therefore very data dependent. This resulted in initial trials where the displacement estimates rejected due to low NCC were clearly inferior to those found from the discontinuity reject factor (figure 8.17).

²a single pixel can be reasonably expected to score a NCC value close to 100%, albeit an inaccurate displacement estimate. Larger blocks result in inclusion of more context but also, more error on average across the whole block

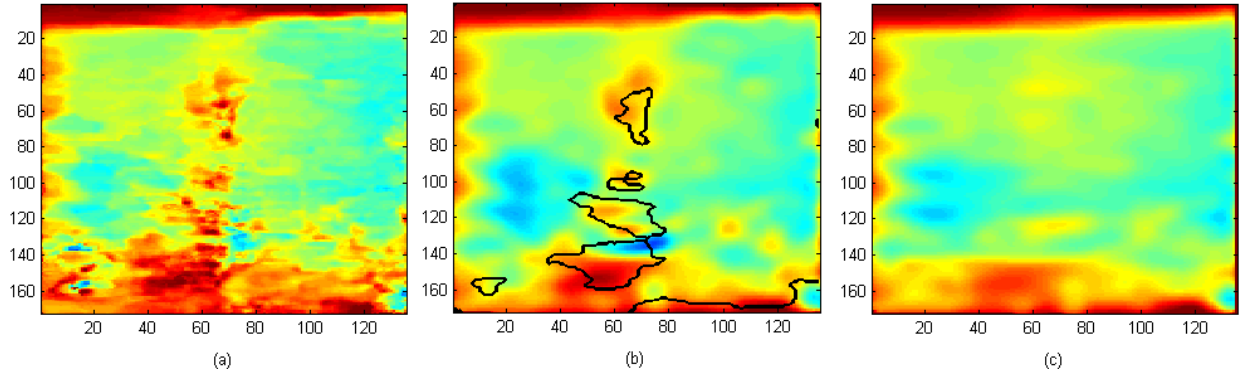


Figure 8.17: Example of lateral displacement estimation images (a) No regularization, discontinuity present due to shadow (b) Reject factor ignores any estimates with $NCC < 0.8$ within the black contour lines (c) Linear fit reject factor as previously described.

8.5 Chapter conclusions

This chapter has investigated different levels of displacement field regularization by three different parameters and used this to investigate the quantitative and qualitative effects on synthesized, phantom and *in vivo* Achilles tendon rupture data. The method used smoothing splines to produce a 2D bicubic approximation function which can efficiently be used to assess the strains in the full field of the displacement image.

Some potential concerns have been highlighted which could have impact upon future studies and upon quantitative elastography in general. The following conclusions can be drawn:

- Over smoothing has been shown to reduce the effective resolution of the strain estimation field, although unregularized field is highly affected by noise.
- Over regularization by overly-aggressive outlier removal of large areas of displacement image can produce mean strain values that diverge away from the true value.
- Highly regularized strain fields can reduce the maximum peak and mean strain.
- Lateral strain fields from patient groups in the data became less distinct from each other as regularization is increased.

Yet some clear benefits can be seen from regularization that could enhance the accuracy of measurements:

- Smoother lateral strain fields which are less dependent upon region of interest selection.
- Reduced or removed large shadow artefacts and small discontinuities.
- Preservation of mean lateral strain values for low levels of regularization.
- Fewer erroneous high strains to which significance could be attributed.
- Reduction in variation of lateral strains measured in the rupture patients during early weeks.

Chapter 9

Summary and Future Work

9.1 Summary

This thesis has presented innovative contributions to the field of using lateral ultrasound elastography to measure function and healing from rupture in the Achilles tendon.

It has been established that there is a pressing demand for objective, functional measures of healing of the Achilles and other tendons for clinical and biomechanical research uses. A new, accurate and repeatable measure could greatly aid the development of new treatments, help to guide treatment of individuals and ultimately diagnose conditions before rupture occurs. The approach to the contributions here has been akin to initial development work in product design. Real *in vivo* data was used from the outset in order to better assess the difficulties with lateral strain imaging of ruptured Achilles tendons. The AutoQual algorithm was presented to address some of these difficulties and benchmark tested against another algorithm. The input parameters were then investigated and optimised before using the algorithm on a patient study to further assess its potential benefits. Then the remaining imaging artefacts were catalogued, and an investigation of regularisation as an additional tool for mitigating shadow artefacts was conducted finding that it could improve image quality but risks negatively impacting on quantitative analysis.

The AutoQual algorithm was presented as a novel strategy specifically designed to improve the accuracy of image-lateral displacement matching for ruptured tendons. The use of bicubic spline signal interpolation, quality determined search, adaptive block size and automatic search range is a unique combination which is highly complementary for this task. The performance was demonstrated quantitatively with phantom block experiments and was superior over a previously existing multiscale elastography method, with lower normalised square measurement error of lateral strains induced, more uniform strain fields at high compression speeds and similar performance for rigid body motion. It was then

demonstrated that the AutoQual algorithm showed superior qualitative performance on *in vivo* examples, with lower standard deviation of strains estimated and higher normalised correlation coefficients of block matches found.

Optimisation of the AutoQual algorithm provided an opportunity to investigate and more fully describe some of the contributing functions and the design decisions taken in their implementation. Seed point position was shown to be more simply implemented in this application than in the scenarios used by Chen et al. with their quality determined search algorithms [179, 180], and it was found that placing seed points 10% of the image height from the top, where image strength is good, to be acceptable. Different cost functions were trialled and it was found that SSD costs were more likely to produce small discontinuities which were eliminated with NCC. Spline functions were interrogated and, despite a less intuitive motivation for using cubic splines with allowed overshoots in the lateral direction, splines without overshoots were shown to increase the variability of performance. Strain window size was investigated and found to increase smoothing of the lateral strain estimation field. Setting different values for the automatic search range produced minimal differences, which is encouraging as it implies robustness of the algorithm for the strain rates tested. Matching block size had a greater impact with greater smoothness of the strain field but also greater (underestimating) strain error for larger blocks.

Armed with a new tool with proven improvements to accuracy and consistency for this application, the AutoQual algorithm was used on a 24-week longitudinal study of 21 patients suffering from Achilles tendon rupture. This demonstrated that lateral and principal strains from controlled passive dorsiflexion are measurable and change over the course of healing as the mechanical properties change. The lateral strains measured during controlled passive motion were quantitatively more repeatable and more sensitive to changes over time than axial strains found from manual palpation of the probe. Lateral and principal strain measures of the whole patient group gave Spearman rank correlation coefficients up to 0.72 and up to 0.80 for principal strain divided by cross sectional area (ϵ_p/CSA). One patient that reruptured their tendon also produced a notable change in response in their lateral and principal strain measurement values which was not seen in

the clinical scores (VISA-A and ATRS). These clinical scores did, however, distinguish between treatment groups, while the strain measurements remained inseparable. This finding was consistent with conclusions from Schepull et al. that used a different method to measure strain [112]. As well as the primary results, this study provided a comprehensive overview of the healing process and ultrasound elastography for engineers that may be unfamiliar with the clinical and imaging issues.

The experience with the longitudinal study highlighted that there are image artefacts that can be misleading, especially if location point-values of strain are taken from the strain image rather than region of interest mean values. The artefacts described were: displacement error variation, bone region decorrelation, discontinuous tissues and slip boundaries, shadows, out of plane motion and fast motion decorrelation. These were described in detail in order that they can be better recognised and mitigated, and their effects upon the imaging quality and the quantitative strain estimates were assessed. Shadow artefacts from surgical suture knots or haematoma were particularly highlighted as a concern for both lateral-strain image quality and for quantitative impact.

Finally, regularisation was investigated as a tool to address the image artefact issues previously highlighted. A regularisation method using bicubic smoothing splines to approximate the displacement field and generate the spatial derivatives used for strain images was presented, with weight factor, sharpness factor and reject factor parameters. The response of the strain field to changes in these parameters was tested on synthetic, phantom and *in vivo* data to investigate random error and shadow artefacts. It was found that signal-to-noise ratios were improved by all three factors. Reject factor (which discounts outlier displacement estimates) impacted most strongly, effectively removing the visual impact of large discontinuities in the displacement image caused by shadows, while sharpness factor eliminated only small discontinuities. However, reject factor did minimally affect mean strain values at low settings and gave high strain errors for faster strain rates (above approximately 0.3% strain/frame). Aggressive regularisation settings were also shown to reduce sensitivity of the longitudinal patient study results, with lower Spearman rank coefficients and greater overlap of week-by-week groups. Regularisation therefore is a useful tool for improving strain image quality and removing the impact of

shadow and random error artefacts, but care needs to be taken as it can negatively impact upon quantitative strain measurements.

By using real *in vivo* data from patients suffering from tendon rupture, the methods presented in this paper are significantly distinguished from other groups which only attempt to track motion in ultrasound sequences of healthy tendons. This has been pivotal to the development of the AutoQual algorithm, its implementation in a longitudinal study, the investigation into the strain image artefacts that are still apparent and the use of regularisation to help mitigate shadow artefacts. Further development of these techniques could raise the quality of output further and take significant steps toward *in vivo* quantitative strain estimation being a useful clinical and research tool.

9.2 Future Work

Progressing the work presented here toward technology and techniques that are practicable for a multicentre clinical setting requires a substantial amount of additional research and development into the disparate areas covered already - clinical practice, biomechanics and ultrasound imaging technology. Presented here are ideas and some initial results that indicate where progress can be made.

9.2.1 Elastography for biomechanics

Now that substantial efforts have been put in place to improve the quantitative and qualitative capabilities of lateral strain imaging, it can start to be used as an investigation tool into the biomechanics of the Achilles tendons. In order to conduct these experiments, there is a need to measure or estimate the tensile force applied to the Achilles tendon. This can be achieved by measuring the force applied within the foot articulating device and applying a mechanical model to calculate the transfer of forces [202]. Such mechanical models can be relatively simple lever-pivot-spring systems and are simplifications of the true force transmissions that occur in the human foot.

The design of the foot articulation device used for controlled passive motion did include a force transducer affixed to the articulating linkage. Its primary function was for safety of the test subject - if the force became too high, an electromagnet on the articulating linkage

would disengage (figure 9.1). The forces induced were logged during the clinical trial of rupture patients, but the force transducer was not calibrated, the temporal resolution of the force logging was low (one point value every 0.5s), the force data failed to record for approximately $\frac{3}{4}$ of the DF/PF acquisitions and spatial measurements of each subject's foot were not collected. Consequently, the conclusions to be drawn from the results derived from this data are insubstantial to be presented as a contribution, but can be useful to guide the further development of using 2D elastography for estimating tensile mechanical properties of Achilles tendons.

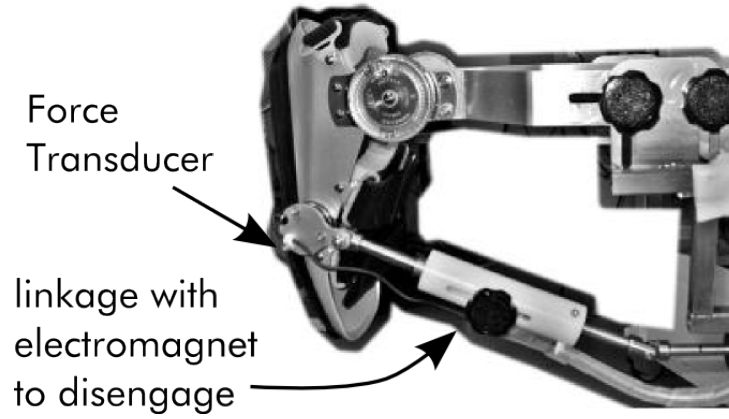


Figure 9.1: *Controlled articulating foot cuff for continuous passive motion with safety linkage and force transducer annotated*

Using the forces measured, the stress of the Achilles tendon can be approximated as:

$$\sigma = \frac{F M_b}{A M_c} \quad (9.1)$$

where F is the perpendicular force measured at the ball of the foot, A is the cross sectional area, M_b is the moment arm length to the ball of the foot and M_c is the moment arm length to the calcaneus insertion (from the centre of rotation).

Force and strain measurement sequences were taken from a single subject (Patient 6) from the clinical study. Ultrasound image sequences were analysed using the AutoQual algorithm as previously described, with the exception that cumulative lateral displacement and strain estimation images were generated at each frame. The tendon region of interest was manually segmented and the mean cumulative strain from these areas was assessed. The moment arm ratio (M_b/M_c) was assumed to be 5 (unfortunately the patient specific

measurements were not acquired by the clinician). The final force measurement was assumed to coincide with the final elastography frame, and force values were interpolated to obtain values at the ultrasound frame capture intervals. Young's modulus was found from a linear fit to assess the gradient of the stress vs. strain data points. The elastic moduli estimates are shown in figure 9.2. These preliminary results showed a high elastic modulus for the healthy tendon and much lower moduli for the ruptured side. Changes over time were visually less distinct than those found by measuring estimated lateral or principal strain alone, and it could be that the error from cross section area measurement (as previously discussed in chapter 4) is affecting the ability to measure changes well. Elastic moduli were considerably lower than those found by Schepull et al using the RSA measurement method, who found post rupture Young's moduli to be 82.3 ± 31.0 MPa and 87.8 ± 33.8 MPa at 7 weeks post rupture. The difference could be accounted for by patient-to-patient variation, the use of relatively low strains, differences in moment arm or cross sectional area measurement or viscous effects from the rate of strain induced. Even considering these discrepancies, a difference between approximately 80MPa and 1MPa seems over large and further investigation is required to see if higher strains can be stimulated to infer more consistent elastic moduli.

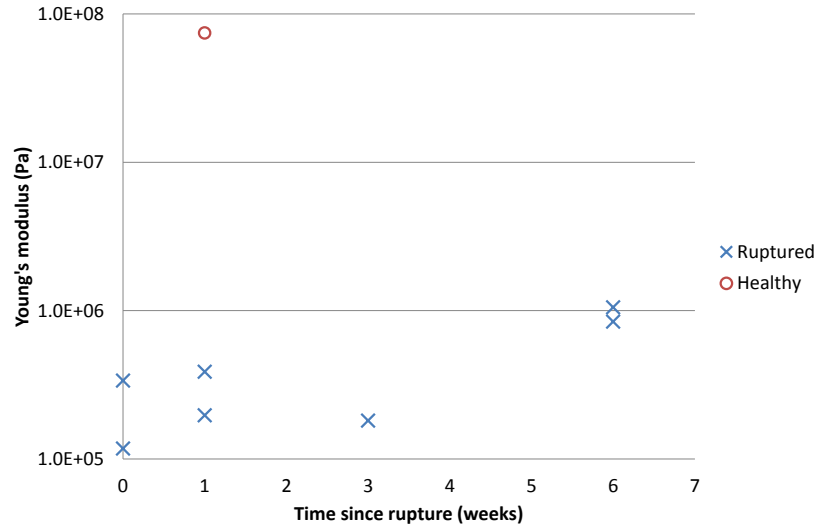


Figure 9.2: *Elastic Moduli estimates from Elastography from Patient 6 of the clinical study including healthy tendon and ruptured Achilles tendon.*

Further calibration, characterising the mechanical errors of the foot articulation device and initial estimation of mechanical properties of healthy tendon under lab condi-

tions were conducted after the clinical study with James Smith (Master of Engineering 4th year student) [203]. The sample frequency of force measurement was increased to approximately 10Hz and there was a greater confidence that the final ultrasound frame temporally aligned well with the final force measure.

Repeated acquisitions showed that consistent measures of Young's modulus were possible (figure 9.3(a)) and that the stress-strain curve was affected by the range of motion that was used (figure 9.3(b)). Further investigations into the effects of acquisition speed, motion range and inter/intra-subject variation are required to draw further conclusions.

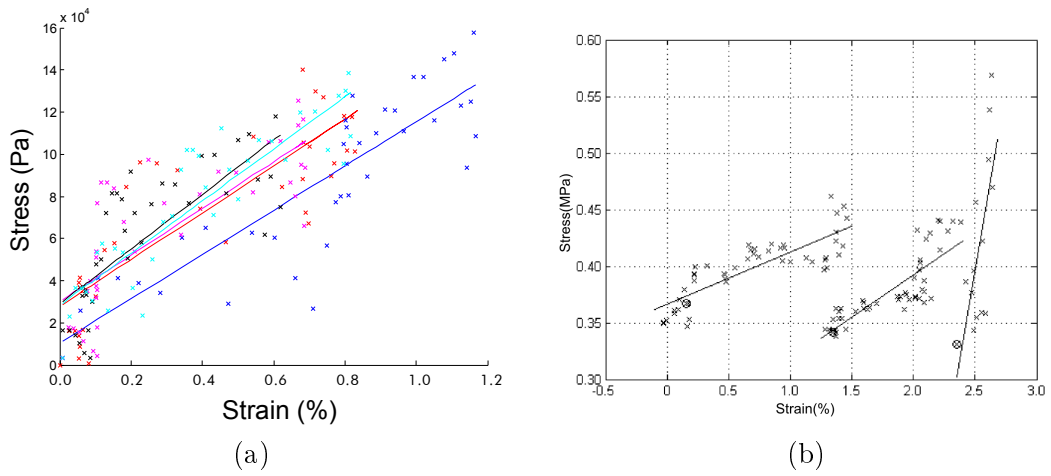


Figure 9.3: *Stress and strain estimates of a healthy Achilles tendon found by automated continuous passive dorsiflexion motion (a) Example of 5 repeat measures. (b) Example of changes in gradient at different pre-strained levels. Reproduced from [203]*

9.2.2 Improvements to foot articulation hardware

Further research has shown that there are commercially available alternatives to the bespoke foot articulation device used that may provide benefits to future work on this project, such as the Kinetec Breva Ankle continuous passive motion (CPM) Machine. Using an existing commercial system could save time and resources in further development and perhaps gain advantages in repeatability of motion.

A level of automation could be brought to simple moment arm measurements, which can be prone to errors - a small error in length measurement to the insertion of the calcaneus (which is not a point measurement as the tendon has width) can lead to large errors in stress measurement. For example, a 1mm error in M_c of notional length 40mm

gives a 2.5% error. Measurement errors of this order are not to be unexpected as accurately determining the centre of rotation is difficult (indeed, the motion is not a pure rotation and has been shown to change the moment arm length throughout flexion [204]) and determining the insertion point accurately is difficult, especially when managing injured subjects. With the presented apparatus, there is the possibility of inferring the calcaneus moment arm length without measuring the patient. If a rotary position (θ) of the foot were recorded (using an encoder or potentiometer) then the moment arm length for small rotations could be inferred from the elastography displacement measurement (d_x) of the Achilles tendon close to the insertion (equation 9.2).

$$M_c = \frac{\tan(\theta)}{d_x} \quad (9.2)$$

It has been shown with phantom experiments that a measurement error can be up to 2.5% at speeds of 2mm/s (chapter 4, section 4.6.1), making it approximately equal to that from a 1mm error in manual measurement. However, it would benefit from increased automation, less work for the clinician and an improved repeatability. An experiment would need to be conducted to prove this concept further.

9.2.3 Higher strain protocols for healthy tendons

Although passive motion has been shown to be sensitive to changes in ruptured Achilles tendons in weeks 1-8, results were less conclusive thereafter. It is speculated that for higher stiffness tissues, too small a strain is being induced to be accurately measured by the current presented method. The existing foot flexion device was developed with recent rupture patients primarily in mind and the motion protocol was conservatively set so as to present minimal risk of pain or damage. Unfortunately, the stepper motor used for the foot plate articulation cannot run faster than that used in the longitudinal study. Sequence length in the Zonare ultrasound machine is also limited to approximately 3.5 seconds.

Two motion types were tried with voluntary motion to assess the viability of large amounts of ankle flexion. *Motion 1* was a voluntary dorsiflexion, lifting the subject's toe (in a similar method to that used by the automatic motion previously described). *Motion*

2 involved the foot being placed against a smooth concrete wall and pushing down in plantar flexion. The angle of the foot to the leg was set at right angles and this was maintained (the push from the foot did not elevate the subject). In both motion cases the subject was lying face down and the only force imposed was generated by the subject's muscles and not from their weight.

Results showed that smooth strain progressions can be obtained from large motions of the foot (figure 9.4).

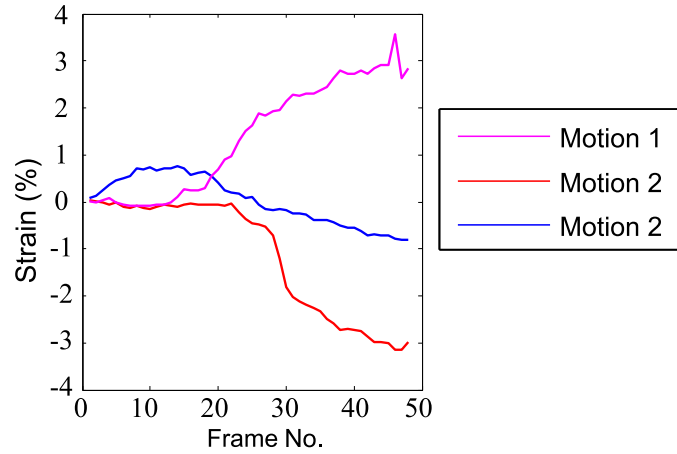


Figure 9.4: *Lateral strains estimated by elastography in a healthy Achilles tendon measured by voluntary high-force flexion. Movement types ‘Motion 1’ and ‘Motion 2’ defined in section 9.2.3*

This demonstrated the concept that large strains can be acquired within the Achilles tendon with active or passive motion types, and that further work is worth pursuing in making these motion types repeatable and suitable for clinical elastography.

9.2.4 Further AutoQual Algorithm improvements

Further development could be carried out on this algorithm to incorporate the potential benefit of other published strategies for enhancing ultrasound image tracking. There is an upfront desire to improve the computational speed and usability of the algorithm so that it can be applied to ultrasound RF sequences quickly and effectively by 3rd party users and allow it to be used for wider trials and investigations.

9.2.4.1 2D signal companding

The technique of signal companding (stretching or compressing the signal in either one or two dimensions) upon comparison signals and has been shown to reduce noise and improve

accuracy for compression elastography using multiscale techniques [122, 205, 206]. Signal compressions can become significant if large strains are applied or large block sizes are used (figure 9.5). This can cause decorrelation or affect the accuracy of block matching.

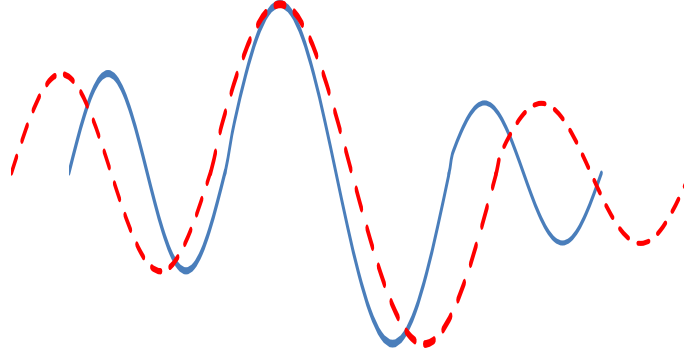


Figure 9.5: *Example of source signal (blue, solid) and stretched signal (red, dashed) demonstrating that the total error of a signal correlation increases with larger samples or higher compressions.*

The signal companding method involves synthetically manipulating the image in the post time-frame to account for the amount of strain that the material has undergone and therefore provides a more accurate match with the signal in the prior reference frame. The difficulty with the technique is it potentially adds another inverse problem into the formulation: As the amount of strain is not known at first we cannot accurately account for it until we have measured the strain. Previously existing algorithms [117] involve either assuming a constant strain for the whole field (suitable for repeatable compressions or repeatable tensile stretches of a single body in the field of view) or performing block match searches iteratively where the subsequent attempts are distorted by the strain found previously. This has been used effectively in 2D strategies previously [117] and could assist accuracy which would be of benefit for stiffer tissues such as healthy tendon.

The use of spline coefficients in the AutoQual method would lend itself well to this, as point values from the signals could be simply interpolated from adjusted positions with minimal extra computational effort. Viola et al. stipulated this in their paper [144] and commented that this could also account for rotation. Sadly, changes due to large rotations are less likely to be compensated for, as the appearance of tissue is direction dependent. The additional computational cost and numerical difficulty involved with adding an additional rotation variable to the block matching algorithm may also be prohibitive.

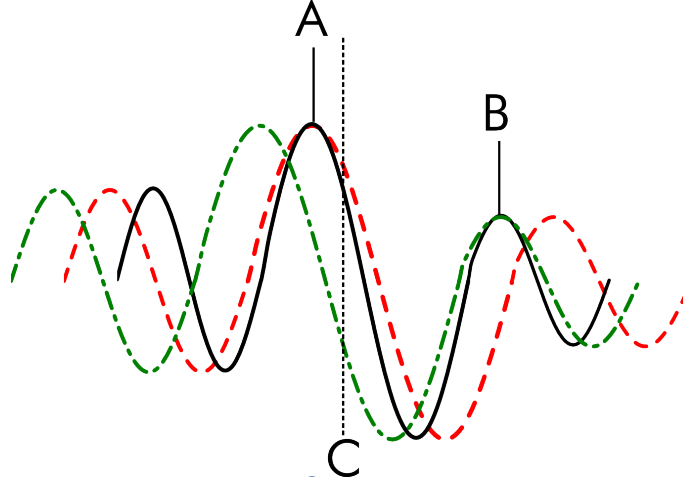


Figure 9.6: Example of source signal (black solid line) and two stretched signals (red dashed line aligned to peak ‘A’; green dot-dashed line aligned to peak ‘B’) demonstrating that when compression is significant alignment to central pixel ‘C’ is not prioritised.

9.2.4.2 Importance weighting during block matching to aid accuracy or remove shadow artefacts

One of the issues that signal companding solves is that of ‘peak alignment’. If the signal block being compared between frames is long and there is a compression or tension applied, then some of the peaks and troughs will become inherently out of phase. This issue becomes more significant for larger block sizes or greater compressions. When matching the blocks there is a chance that the maximal alignment will occur at some distance from the best central pixel alignment position (figure 9.6).

Importance weighting of the NCC values is proposed as a method to improve the alignment to important pixels. Here, the NCC is multiplied by a weight so that those in the central region have greater significance to those in the outer regions (equation 9.3).

$$NCC_w = \sum_{i,j} \frac{W(i,j)s_1(i,j)s_2(i,j))}{W_{max} \sum_{i,j} \sqrt{s_1(i,j)^2 s_2(i,j)^2}} \quad (9.3)$$

where s_1 and s_2 are the RF signal blocks in successive frames and W is the 2D weight function.

Initially, a 2D Gaussian distribution was proposed as a weight function to initially test the concept using the phantom block decompression experimental data from chapter 4. An example of the contributing correlation quantities from a sample of two 2D RF signal blocks are shown in figure 9.7.

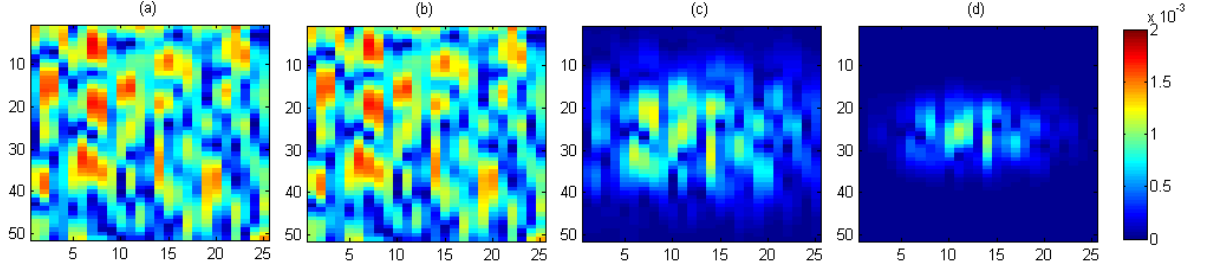


Figure 9.7: Example maps of the contributing NCC quantities from matching blocks of two successive 2D RF frames, modified by 2D Gaussian distribution with (a) no modification (b) $\sigma=100$ (c) $\sigma = 10$ (d) $\sigma = 5$

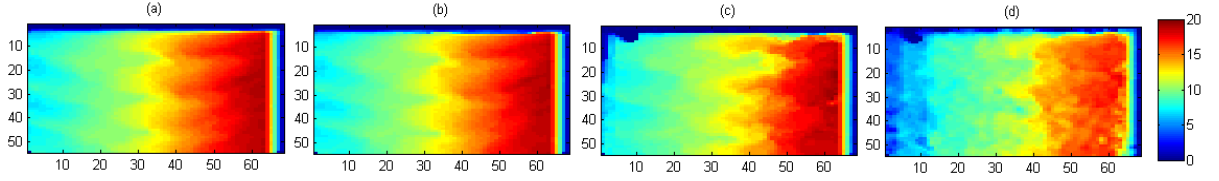


Figure 9.8: Example displacement estimation images of 4.6% strain on phantom block at grip-to-grip speed of 5mm/s, NCC cost modified by 2D Gaussian distribution with (a) no modification (b) $\sigma=100$ (c) $\sigma = 10$ (d) $\sigma = 5$

This pilot experiment was conducted using RF data sequences from 4.6% decompression at grip-to-grip speeds of 1mm/s and 5mm/s had displacement and strain fields estimated by the modified AutoQual algorithm with NCC contributing costs multiplied by a 2D Gaussian kernel (created by the Matlab function "fspecial") with standard deviations of 1, 5, 10, and 100. Results of the displacement and strain estimation fields were assessed qualitatively.

At this stage it is only apparent that low σ values (very high importance to central pixel NCC) greatly distorted the displacement (and therefore strain) estimates - the modifier greatly negated the benefits of a large block size (figures 9.8 & 9.9). The effect of higher σ values was minimal, but this may be due to low compression amounts used in this experiment.

Further investigation is required to establish if there is any benefit to be had from central pixel importance weighting above that already achieved by the Quality Determined Search and Automatic Search Range functions already in place in the AutoQual algorithm, but early indications from this test suggest benefits would be minimal.

However, there is an additional potential benefit, in that the importance weighted matrix can be used in conjunction with a shadow detection strategy. Here, both frames

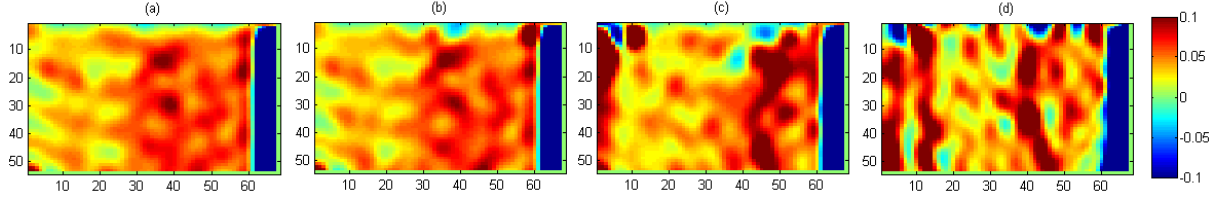


Figure 9.9: *Example strain estimation images of 4.6% strain on phantom block at grip-to-grip speed of 5mm/s, NCC cost modified by 2D Gaussian distribution with (a) no modification (b) $\sigma=100$ (c) $\sigma=10$ (d) $\sigma=5$*

could have shadow detection performed, such as in the graph based method described by Karamalis et al [201]. This approach presents an opportunity to perform displacement tracking that greatly reduces the influence of shadows without the need to regularise. This may aid preservation of strain image resolution. However, such a method relies on an accurate method of assessing signal continuity which would need to be separately assessed.

9.2.4.3 Multi-body tracking

One substantial issue with the current AutoQual algorithm output is the need to interpret regions by manual segmentation. Inaccuracy can lead to errors in average strain estimation, principally due to tissue boundary slip contributing infeasibly large strains. Multibody tracking is a proposed two-step process whereby a low resolution displacement estimation image (widely spaced blocks) is created, and separate bodies within the field of view are automatically delineated. These are then analysed by the AutoQual algorithm separately, reducing the influence of boundary tissue. This is of particular significance for healthy Achilles tendons and for smaller tendons where the small size of the tendon means that boundary influences are much more significant. The Adaptive Block Size feature will be invaluable here as it will allow continued use of large matching blocks where possible but still retain ability to track blocks close to tissue boundaries. This will, however require a substantial reforming of the AutoQual algorithm which currently assumes a rectangular grid of block centre positions.

9.2.5 Improvements to the phantom block experiments

The phantom block testing was a good quantitative measure for performance in areas of high signal strength and provided a benchmark test for comparative accuracy between the Multiscale and AutoQual algorithms. However, it did not provide insights into accuracy of signal performance, for which this Author was largely reliant on qualitative data from *in vivo* examples. If a gelatine phantom block was made with talc scatterers deliberately mixed poorly, a phantom that is mechanically homogeneous, but would appear to have differences in texture (and, importantly dark areas with minimal scatterers) could be made. This may complicate experiments and make them less reproducible but would provide a quantitative assessment of the algorithm accuracy.

9.2.6 Other tendon tissues

Other tissues in the body would also benefit from quantitative techniques to assess damage or healing levels. Each, however, has a different set of requirements and complications. The rotator cuff is a complex structured tendon in the shoulder that attaches to the scapula (shoulder blade), and has high rates of damage due to sport and use. Unfortunately, it is probably the most difficult to assess from any method derived from a 2D ultrasound slice. The complex array of the structure makes a single vector stretch along any sub-structure difficult to control and assess; the tendons are much thinner than the Achilles, forming sheet-like rather than rope-like forms; the supraspinatus tendon is largely obscured by bone. The patella tendon is a more likely candidate for an alternative site to use ultrasound techniques. The tendon inserts into the tibia where it has a roughly oval cross section, then splays into a thinner fan of tendon fibres that pass through the patella (knee cap) and connect to the quadriceps muscles in the thigh. Although the condition of the tendon within the patella (bone) itself is unlikely to be assessable, the tendon region between the patella and the tibia is close to the skin, mechanically simple and suffers from deteriorative conditions and thus may be of value to assess.

Lateral elastography was shown to potentially work for the patella tendon in a trial experiment with (manual) passive motion of the lower leg from a starting position of 90° angle between the upper and lower leg. It has been demonstrated that the lateral motion

image derived from the AutoQual algorithm corresponds well with the position of the patella tendon (figure 9.10(a)-(b)) and that, although the strain estimation image offers few insights (figure 9.10(c)) the cumulative lateral strain from a selected region of interest accumulates to within expected levels of strain (approximately 1%). As with the healthy Achilles tendon, development of suitable protocols that enable smooth, trackable motion of the tendon and forcing up to 4-6% strain levels is key to the use of elastography in future studies.

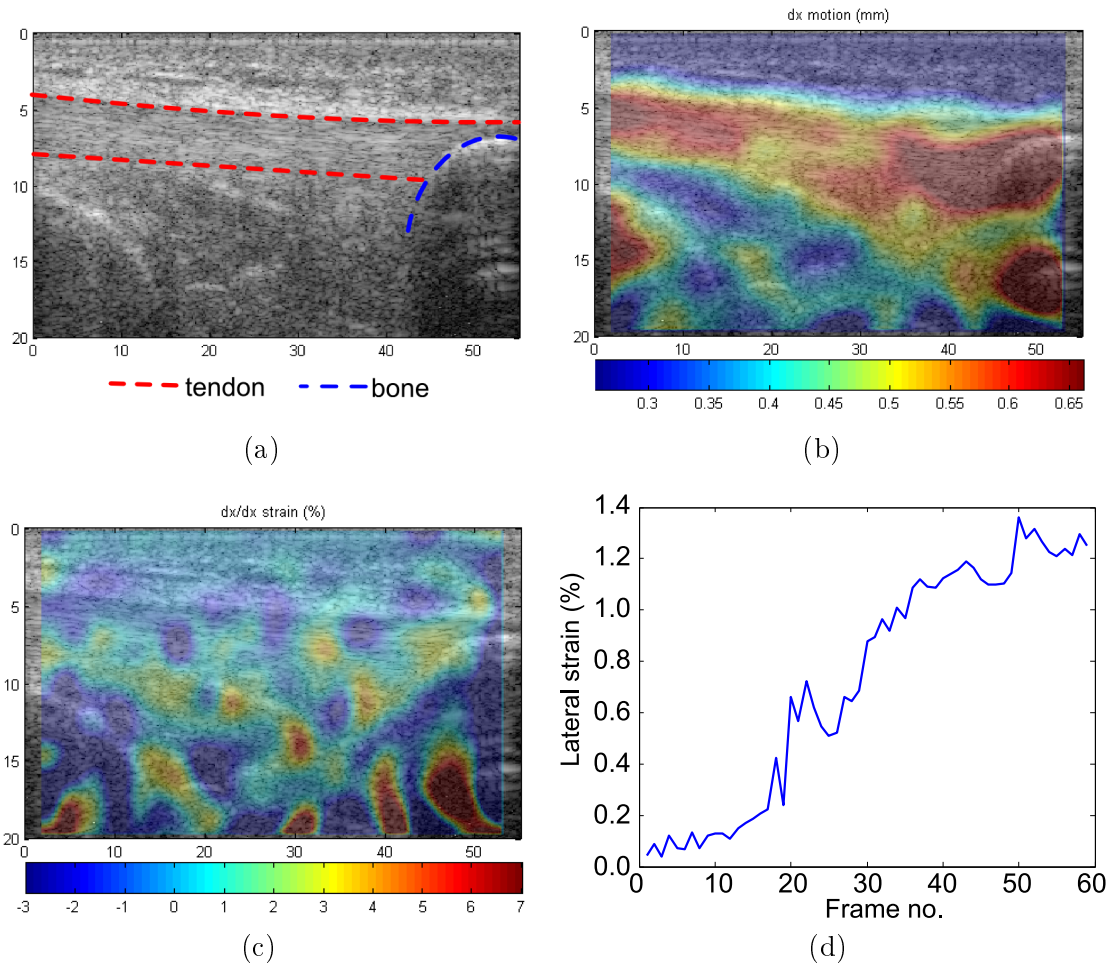


Figure 9.10: *Example elastography results from a healthy patella tendon during passive motion of the lower limb from a neutral position (a) B-mode image. (b) Lateral displacement image. (c) Lateral strain image. (d) Cumulative lateral strain from a region of interest.*

9.3 Final word

This project has been an interesting and diverse study into elastography imaging and quantitative strain measurement of ruptured tendons. The imaging, clinical and biome-

chanical issues have been unique and challenging and it appears that any strain analysis solution will involve a compromise on requirements to obtain meaningful, quantitative results. The findings from this study are encouraging- that lateral tendon strain can be measured *in vivo*, the strains measurably change in the weeks following rupture with controlled dorsiflexion motion and that strains measured by this motion type are repeatable. Imaging artefacts still exist, despite the improvements brought about by the AutoQual algorithm for this application. Regularisation can aid the image quality, but possibly at the penalty of strain estimation accuracy and sensitivity to change over the patient group study used. The future of these lateral elastography techniques will rely partially in the further development of imaging techniques, but also on robust, practical clinical protocols that ensure function strain values are attained during scanning and yet with patient comfort and measurement repeatability maintained. The indications from the future work section are that this is possible with suitable hardware and could help to gain insights into the biomechanical responses of the Achilles tendon and other similar connective tissues. These should focus into three main areas: To further technical improvements of elastography to measure mechanical properties in the Achilles tendon, to develop derivative techniques to be used on other tissues in humans (and possibly animals) and the development of clinical protocols which give the greatest distinction between patient groups and aid diagnosis of conditions.

Appendix A

B-mode images of ruptured Achilles tendons.

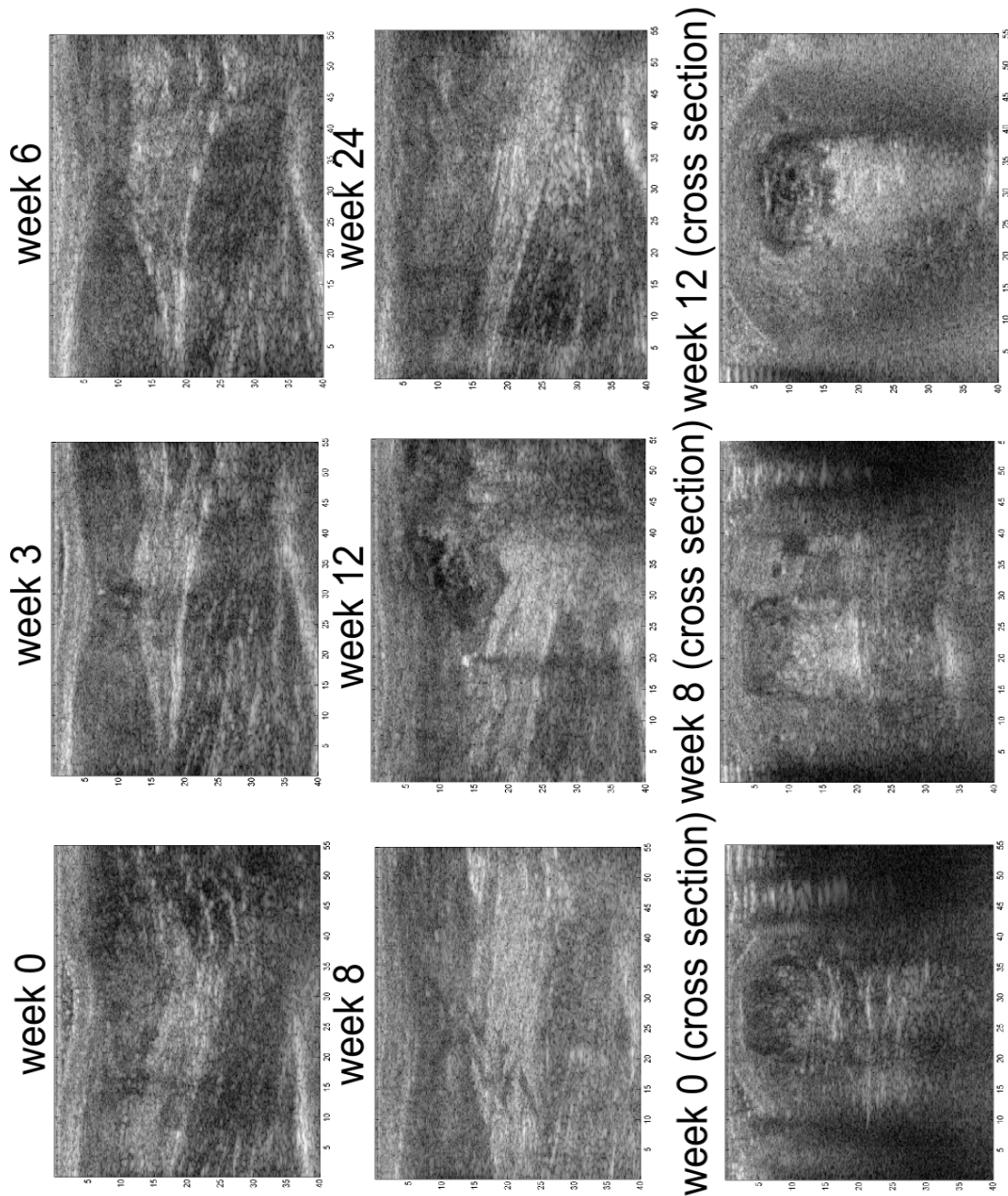


Figure A.1: B-mode sagittal and transverse plane images of patient 6 who experienced rerupture between weeks 8 and 12.

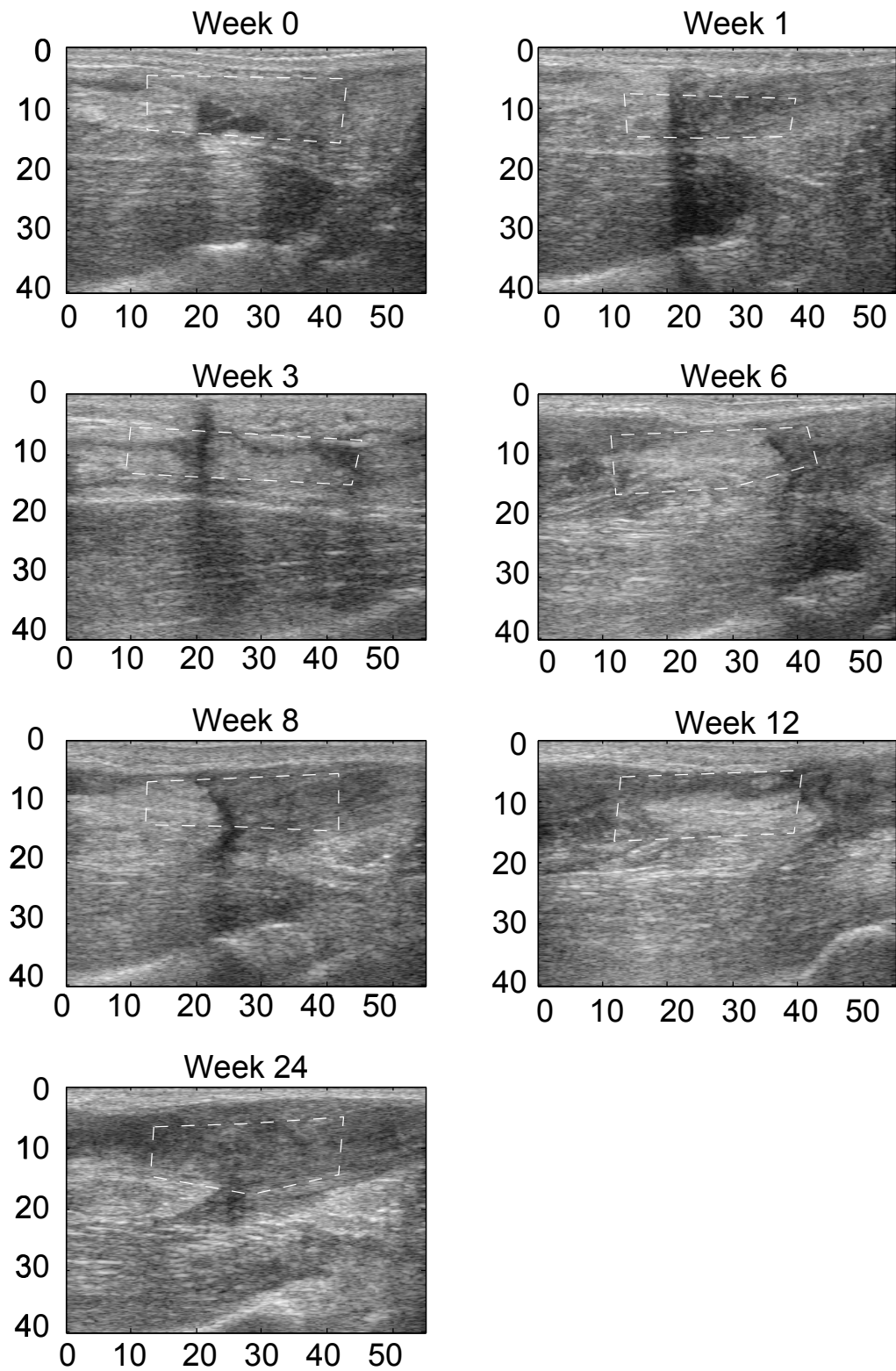


Figure A.2: *B-mode sagittal plane images of patient 7 as healing progressed.*

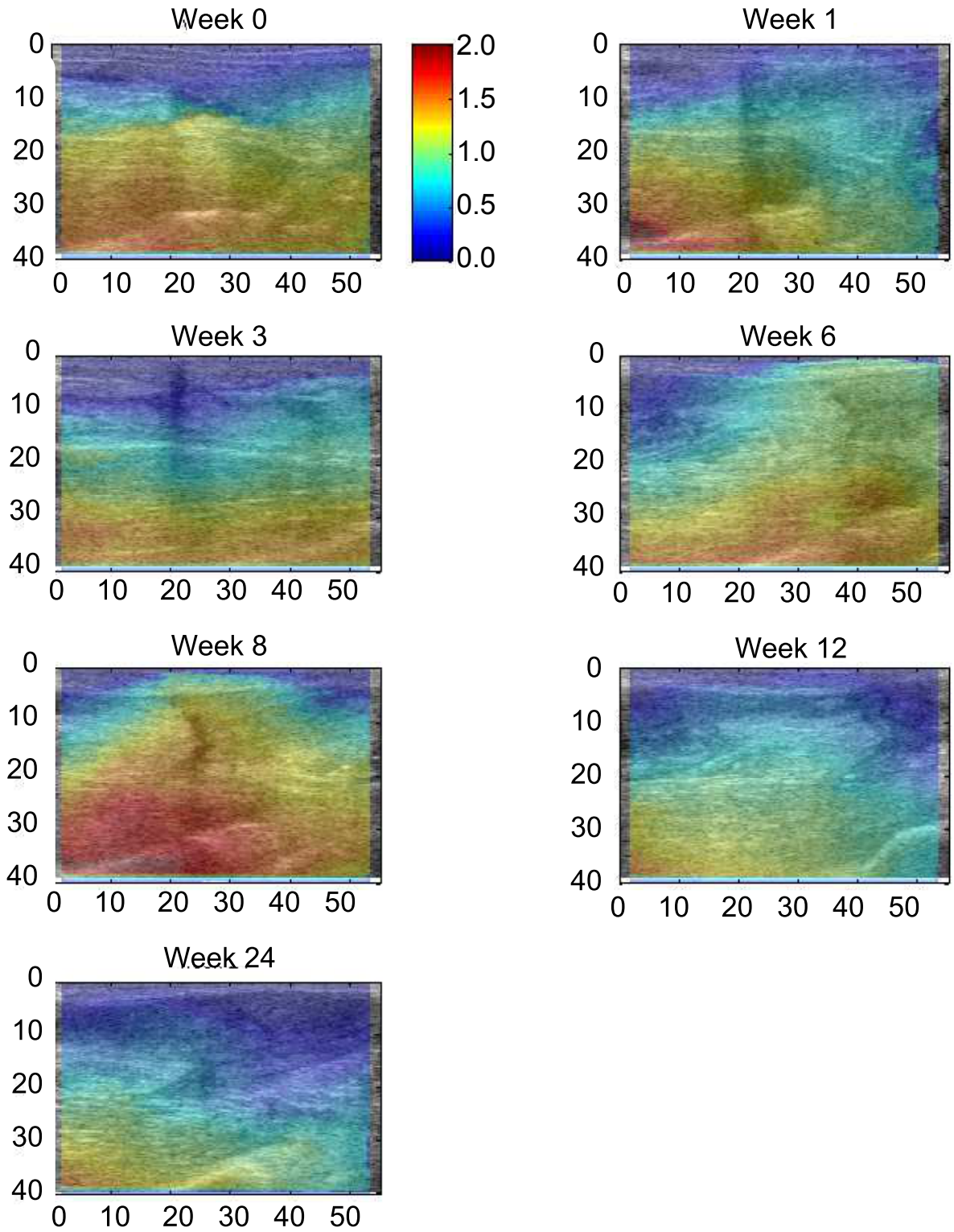


Figure A.3: *Z-direction motion image (mm) of manual decompression motion overlaid on B-mode sagittal plane images (figure A.2) of patient 7 as healing progressed.*

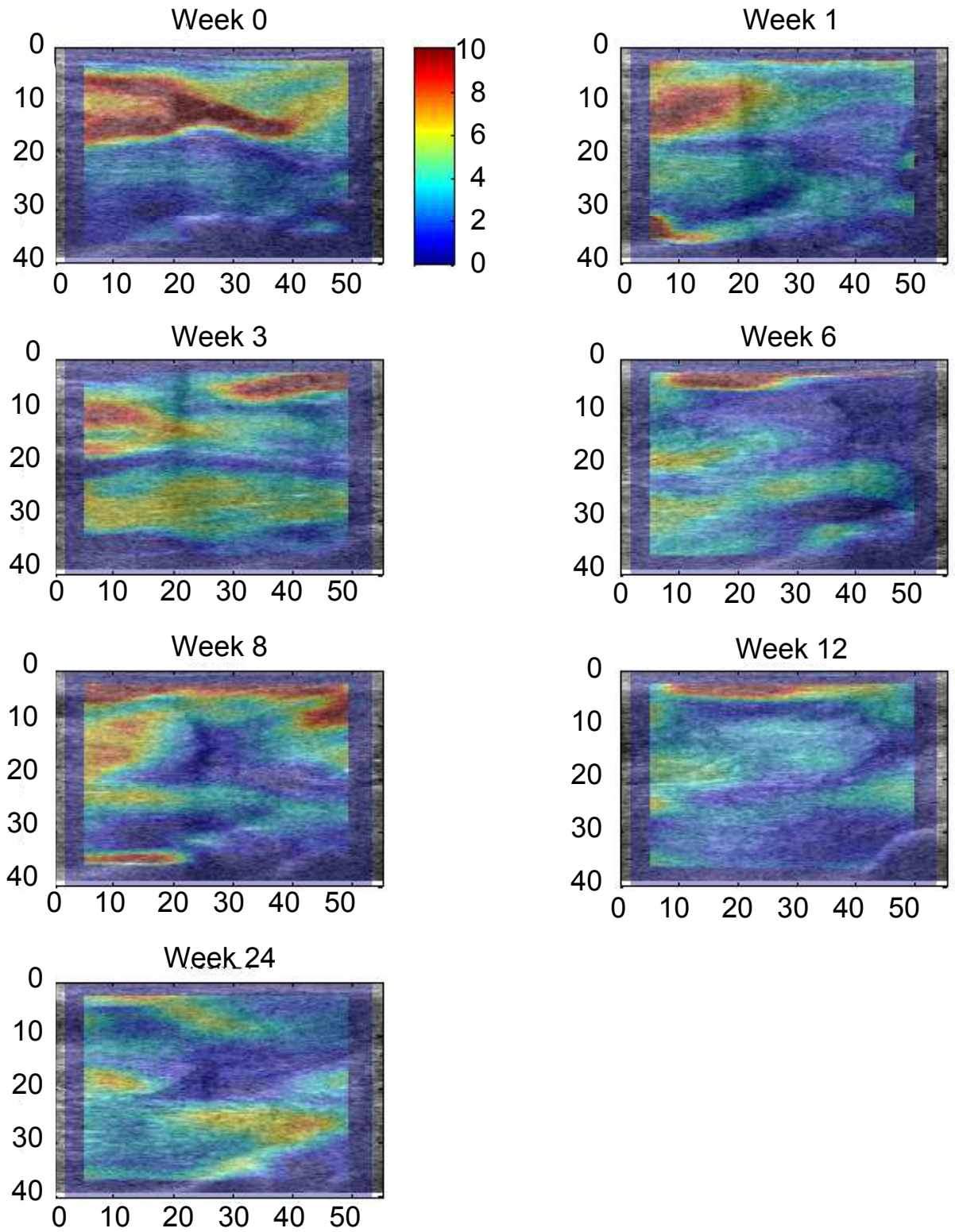


Figure A.4: Z-direction strain (%) image of manual decompression motion overlaid on B-mode sagittal plane images (figure A.2) of patient 7 as healing progressed.

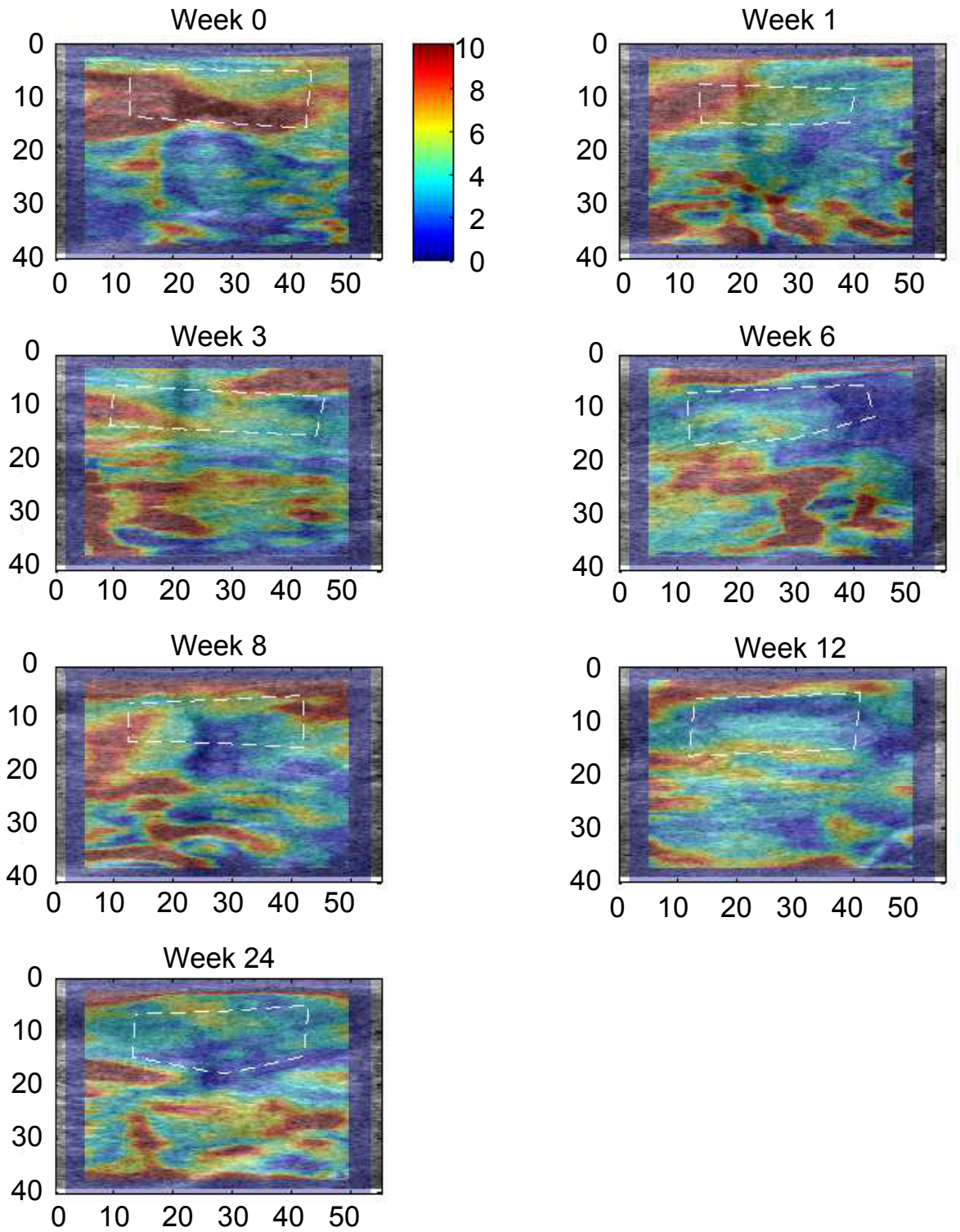


Figure A.5: *Principal strain (%) image of manual decompression motion overlaid on B-mode sagittal plane images (figure A.2) of patient 7 as healing progressed.*

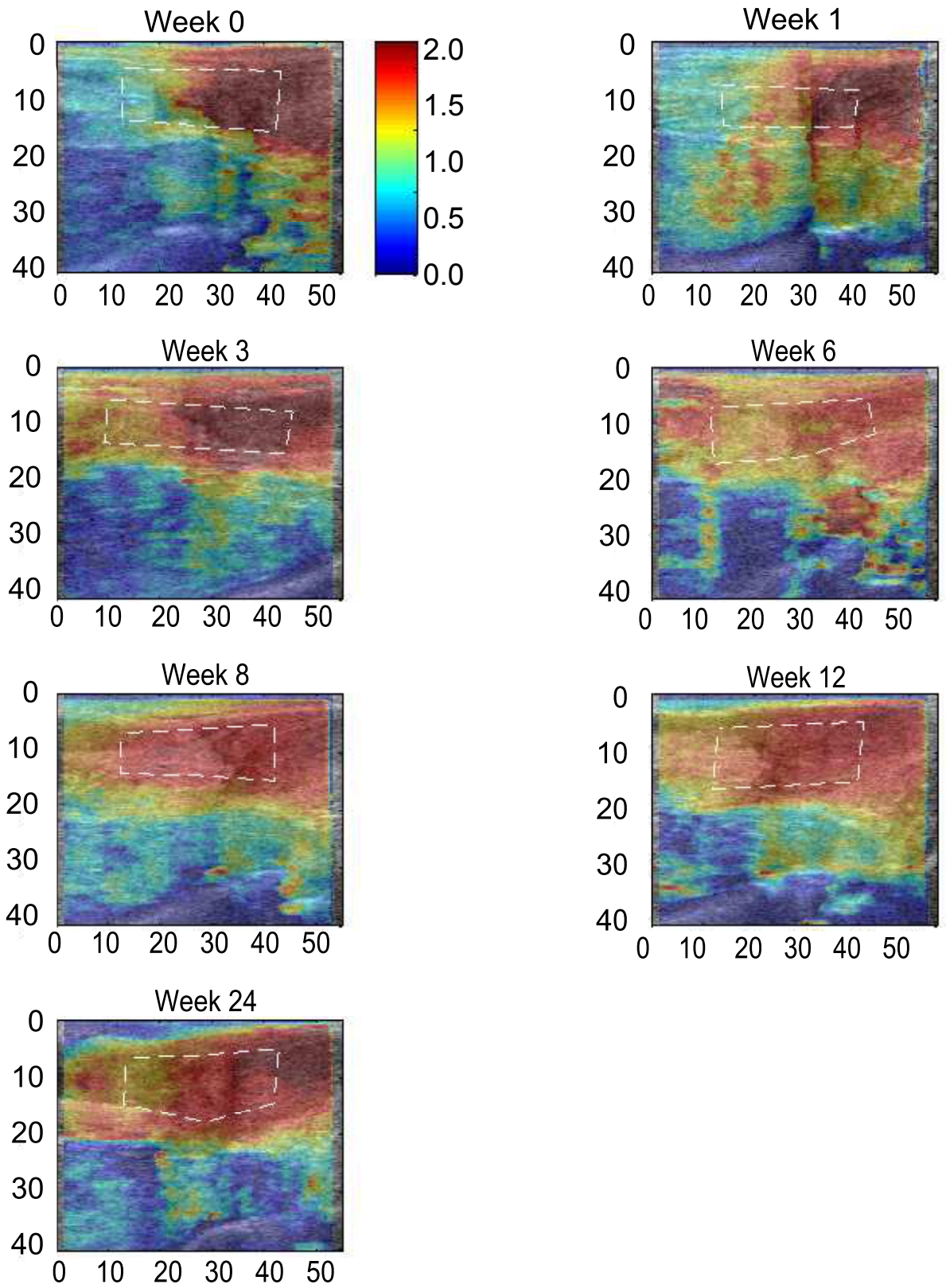


Figure A.6: *X-direction motion image (mm) of passive dorsiflexion motion overlaid on B-mode sagittal plane images (figure A.2) of patient 7 as healing progressed.*

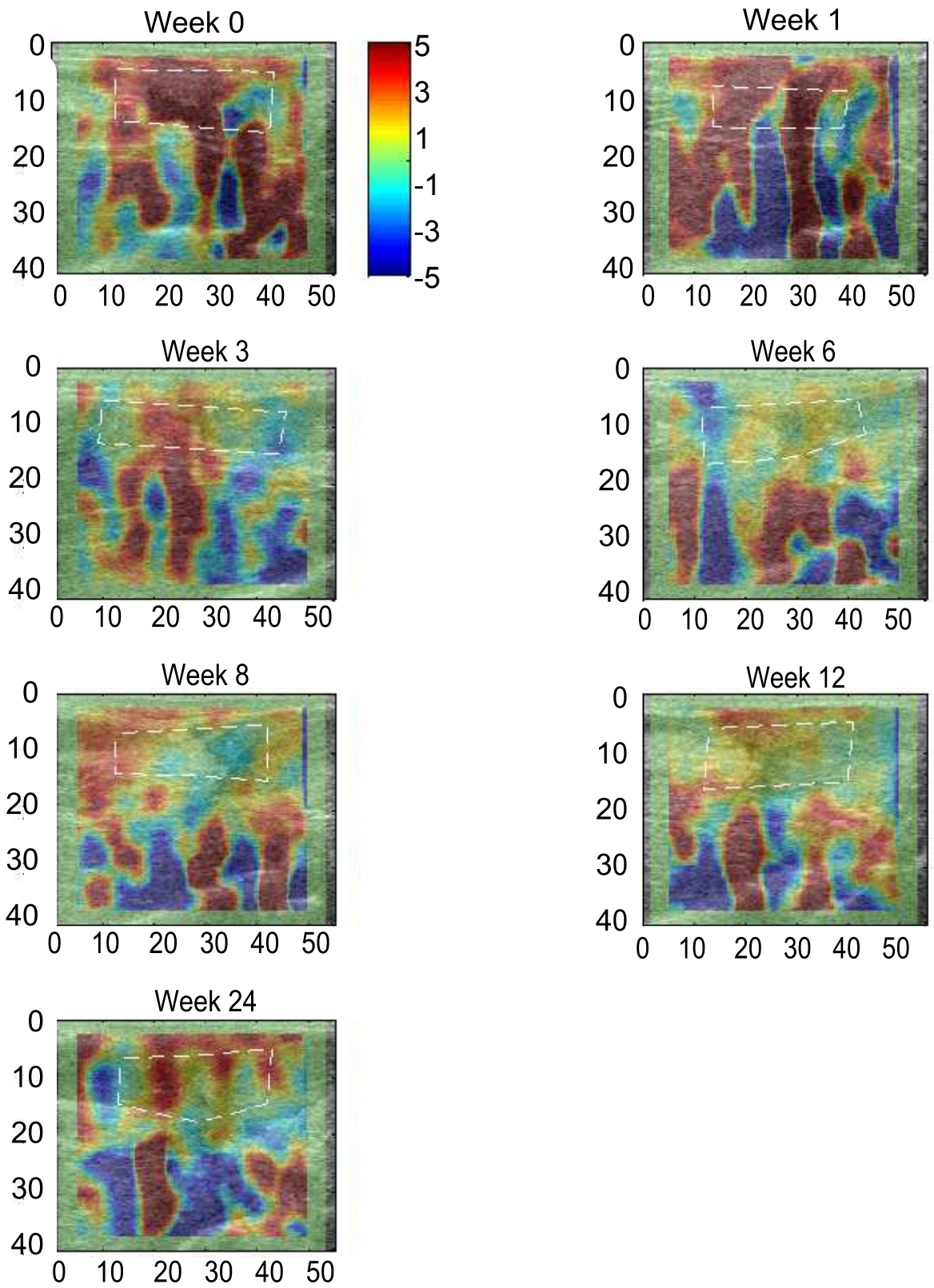


Figure A.7: *X-direction strain image (%) of passive dorsiflexion motion overlaid on B-mode sagittal plane images (figure A.2) of patient 7 as healing progressed.*

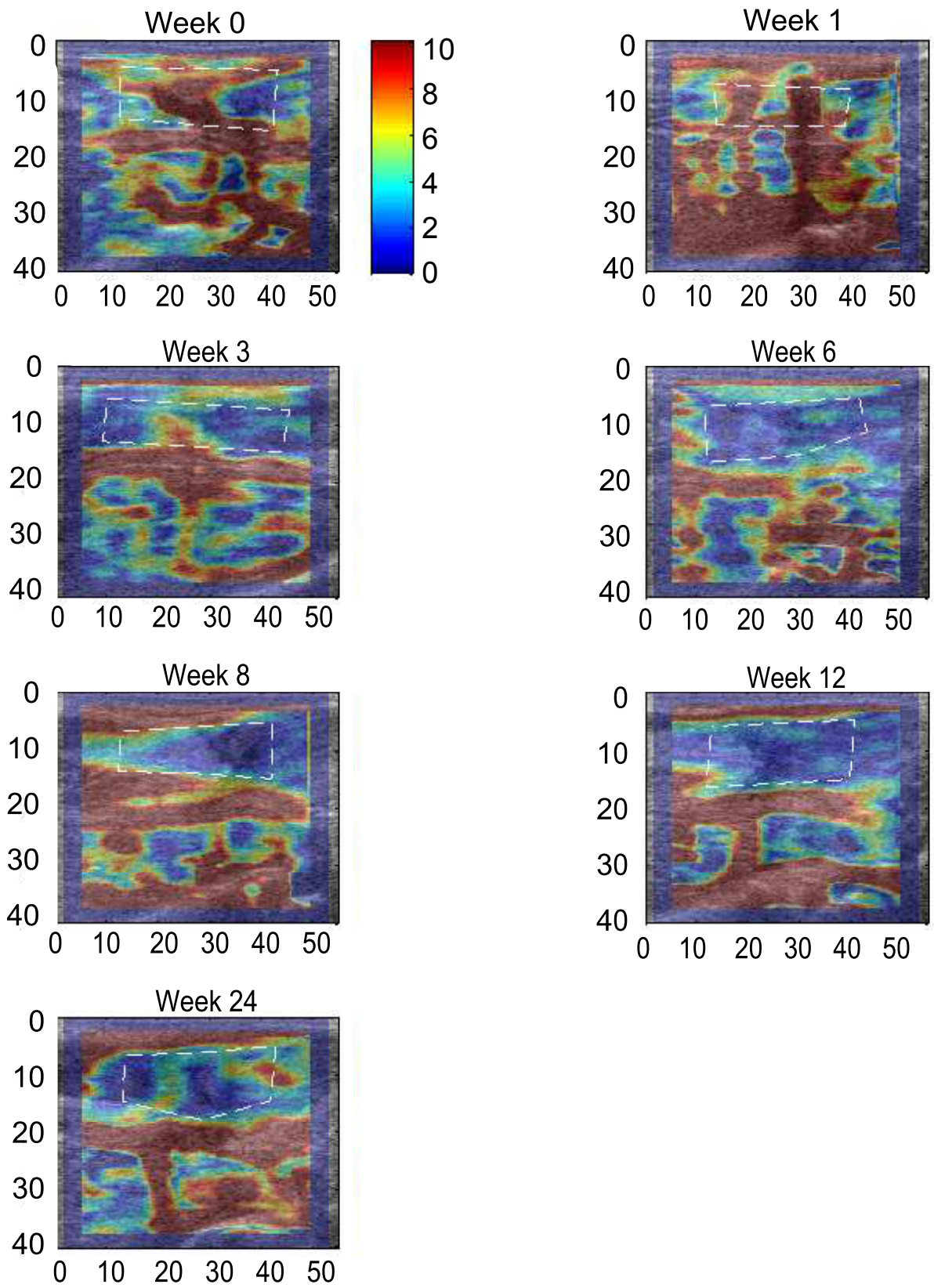


Figure A.8: *Principal strain image (%) of passive dorsiflexion (DF) motion overlaid on B-mode sagittal plane images (figure A.2) of patient 7 as healing progressed.*

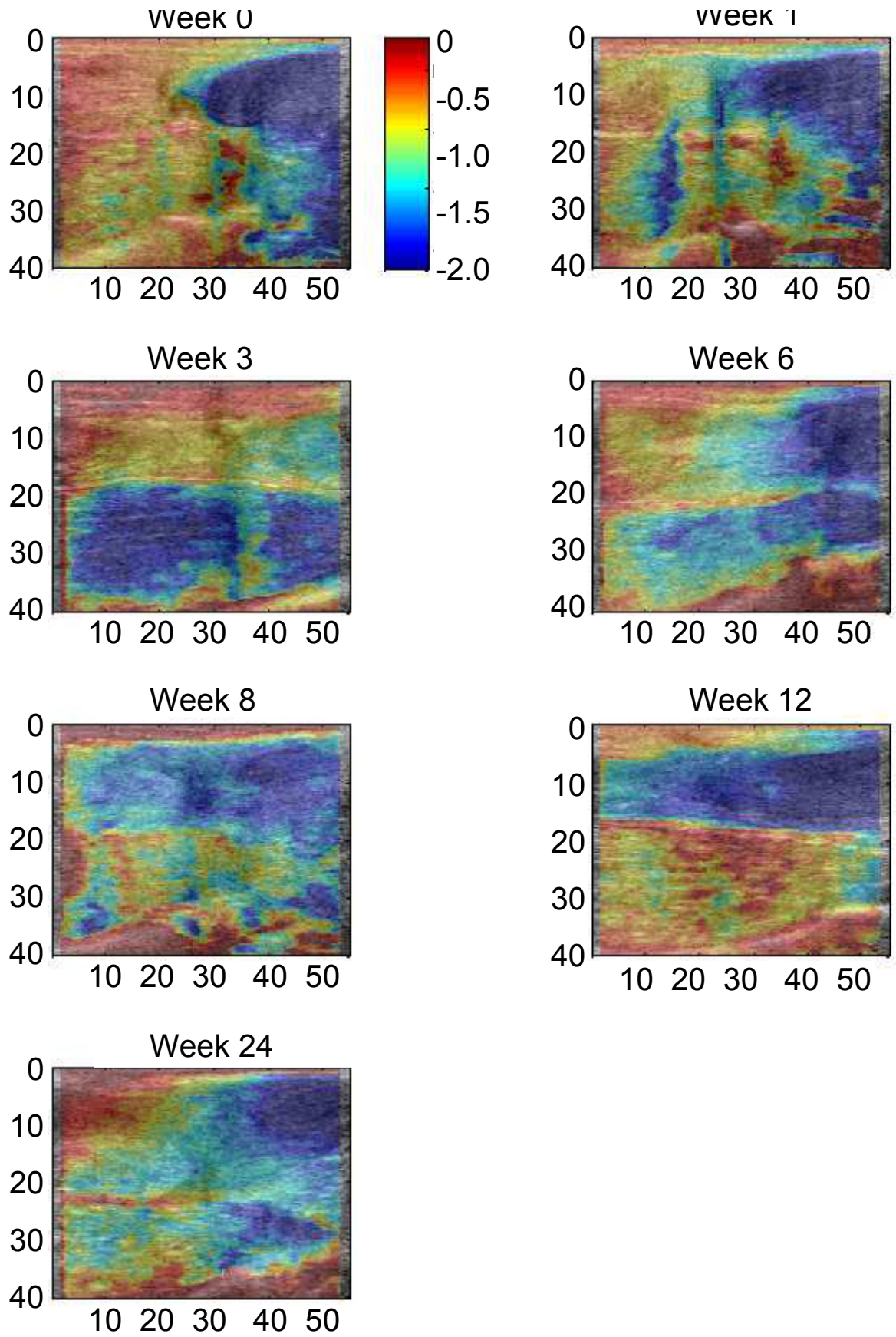


Figure A.9: *X-direction motion image (mm) of passive plantar flexion (PF) motion overlaid on B-mode sagittal plane images (figure A.2) of patient 7 as healing progressed.*

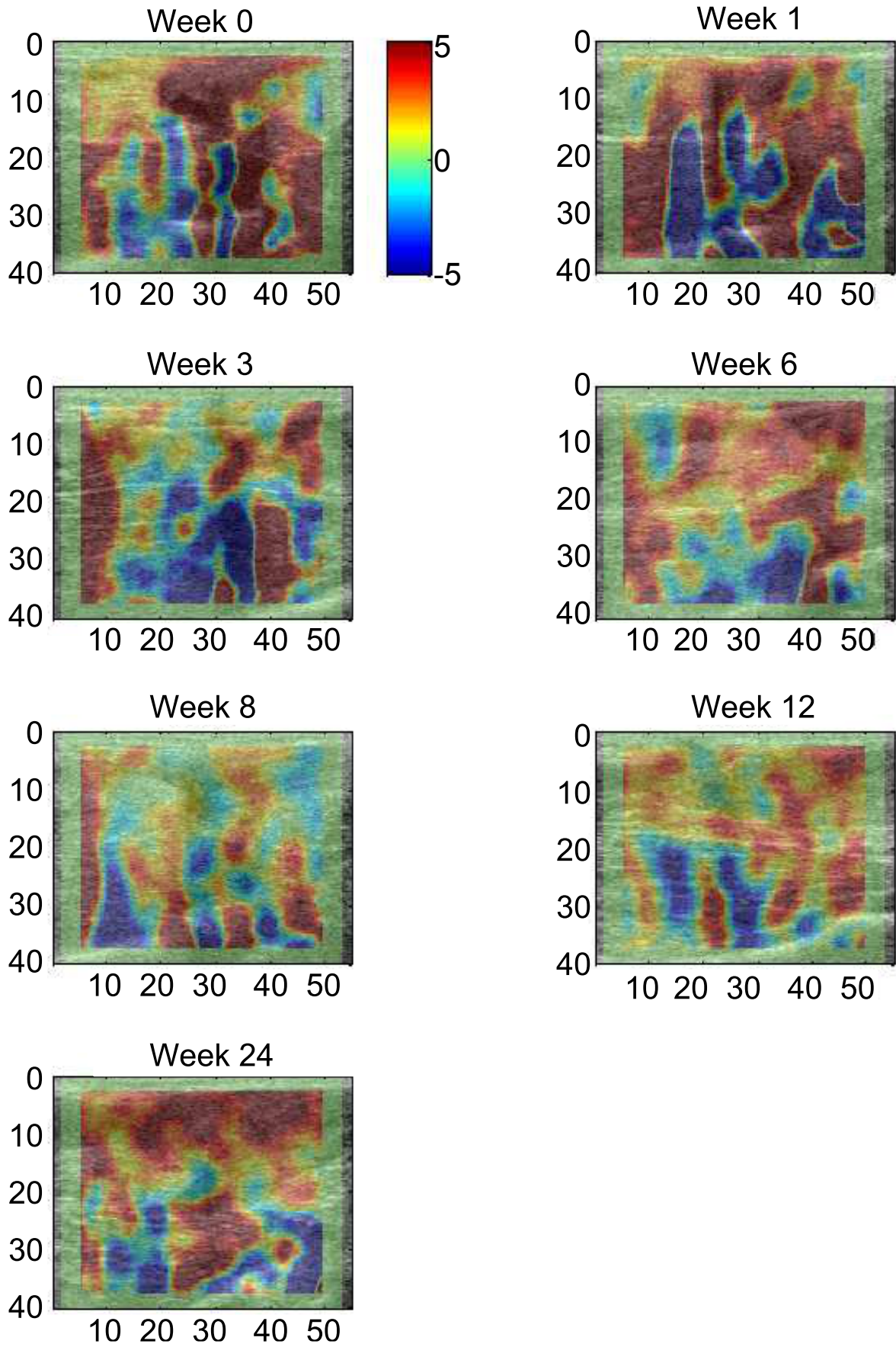


Figure A.10: *X-direction strain image (%) of passive plantar flexion (PF) motion overlaid on B-mode sagittal plane images (figure A.2) of patient 7 as healing progressed.*

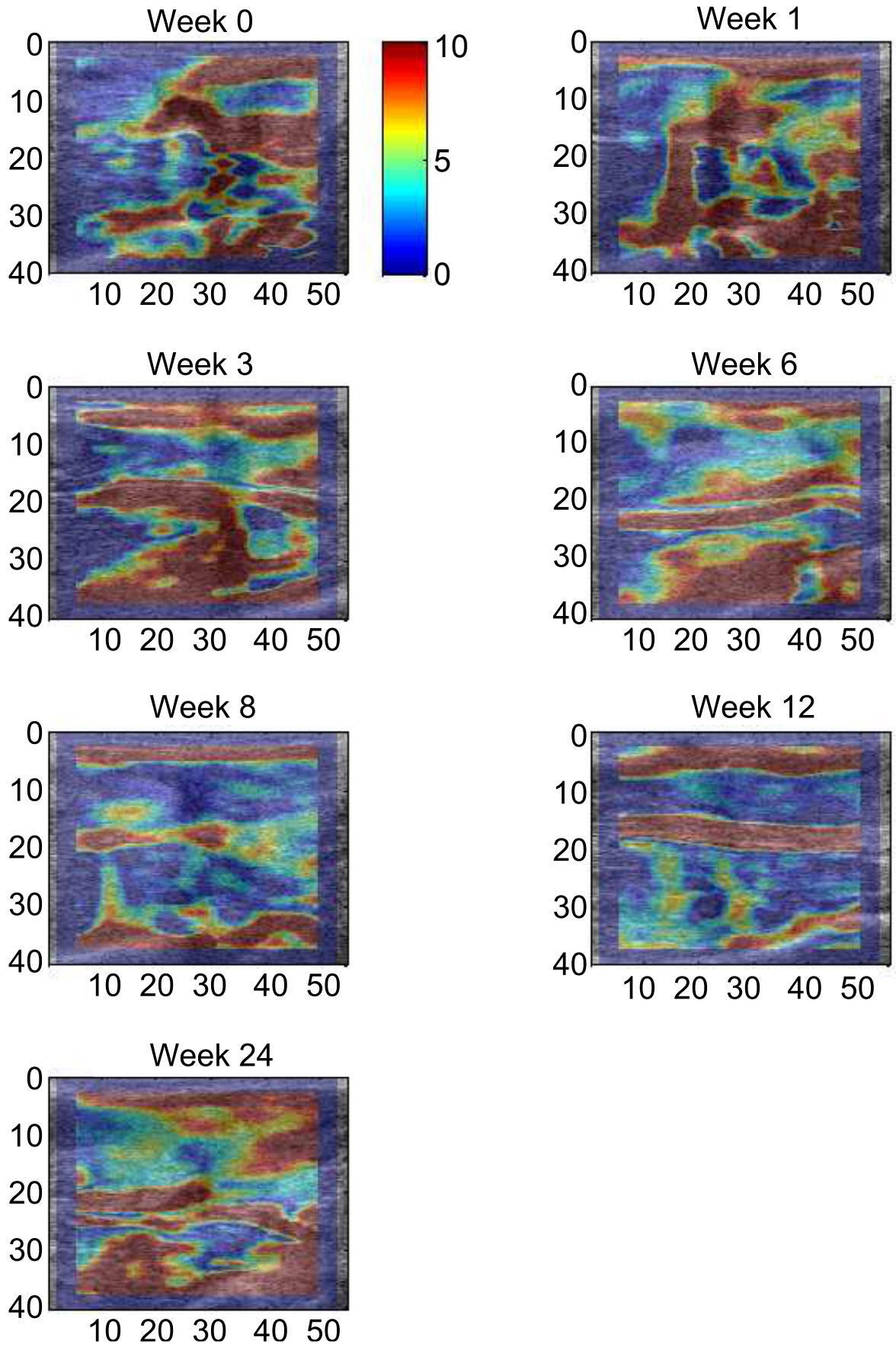


Figure A.11: *Principal strain image (%) of passive plantar flexion motion (PF) overlaid on B-mode sagittal plane images (figure A.2) of patient 7 as healing progressed.*

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