Determination of the Passive Transverse Mechanical Properties of Skeletal Muscle under In Vivo Compression; Experimental and Numerical Aspects

A Literature Review

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Introduction

Before bringing a new product to market, the automotive industry needs to make sure that it conforms to modern safety standards. Car safety can be tested in a variety of ways, of which the most commonly known makes use of the crash test dummy. Another, less costly method to determine safety is by running computer simulations. As input for these simulations, an accurate description of the mechanical characteristics of the tissues of the (human) body is needed.

As part of the HUMOS (Human Modeling System) project a first attempt was made to incorporate some of these characteristics into a computer model. However, HUMOS lacked adequate description of the mechanical behavior/characteristics of (muscle) tissue.

In work package 3 of the EC funded project HUMOS II (GRD2-2001-50053) the knowledge on biomechanical behavior of soft tissues will be improved. The Eindhoven University of Technology is responsible for the determination of the transverse and longitudinal mechanical properties of skeletal muscle during loading up to failure.

In order to get the numerical and experimental aspects operational, a literature study was done to determine the best course of action. First the available experimental methods are analyzed and compared; how to track and visualize the deformation of muscle tissue and how to determine and quantify damage to the tissue. Based on the comparisons a choice will be made with regards to the methods to be used. Secondly, the numerical aspects will be analyzed. Different constitutive models will be discussed, as well as the software packages.

From this literature review and the analyses within, a course of action for the project will be determined.
1 Tracking of deformation

In order to be able to say something about the material properties of muscle, the deformation under an applied load must be measured. Since damage to the muscle tissue is initiated locally [20] data on local deformation is essential for understanding the cause of muscle damage. Several methods have been previously used to visualize the deformation of muscle tissue. One method is the external tracking of deformation using optical markers applied to the muscle surface, in combination with a video setup [03, 20]. More recently Magnetic Resonance (MR) techniques have been applied in the study of tissue deformation [06, 20, g] and direct characterization of properties [04, 10, 16, 18, 38, d, e]. In this chapter these methods, their advantages and disadvantages will be discussed.

1.1 Optical Tracking Methods

All optical tracking methods make use of small markers applied to the surface of the muscle, in combination with a video setup to track the movement of these markers as the muscle deforms. 2D deformation measurements have been done on (partially) excised Tibialis Anterior (TA) muscles of rats [06, 35]. With the aid of an image analysis system local deformation can be determined from the footage of the marker displacement [03]. However, the 2D analysis of curved surfaces leads to projection errors. Calculated strains will also not be accurate due to these errors.

A 3D video analysis of markers attached to the muscle should reduce the errors resulting from a 2D analysis. Such analysis was done [20], however it was determined that superficial strains are not a good measure for deep tissue strains. There is a significant contribution of transverse deformation to contraction deformation; to simulate the distribution of mechanical quantities within a muscle, 2D models should be extended towards a realistic 3D geometry.

The initial geometry of the muscle must be accurately determined to make correct finite element modeling (FEM) possible. It is not possible to do this with optical tracking: the mid-cross-section of the muscle is not visible during in vivo experiments. Because of this, a camera system cannot be used. As will be discussed in subsequent sections, MRI can offer a practical alternative, as it makes obtaining muscle geometry without excising tissue possible [35].

1.2 MR Techniques

Nuclear Magnetic Resonance (MR) is a physical technique that is based, in the case of biological systems, on the magnetic properties of the nuclei of hydrogen atoms (protons) naturally present within the body. The protons have a spin, which produces a small magnetic field, so that they behave like small magnets. When a subject is positioned within the bore of a cylindrical, superconducting magnet, the protons are aligned by the external magnetic field of the MR system in such a way as to create a measurable magnetization of the body, the strength of which depends on the density of the protons in the tissue. In order to produce an image, the magnetization of the body is disturbed by applying a radio-frequency (RF) pulse. As the magnetic field returns to its original orientation, it produces a signal that can be detected by an antenna or receiver coil and used to create an image. This technique has no known ill effects on living tissue [26, 34].
An MR system basically consists of the following components. A large magnet provides the static magnetic field. Radio-frequency coils transmit and receive the radio signals. Magnetic field gradient coils provide the spatial localization of the signal, and with the aid of a computer the radio signal is reconstructed into the final image [34].

There are several ways in which MR can aid in tracking deformation, or help determine the mechanical properties, of (muscle) tissue; commonly used methods for tracking deformation or movement are MR tagging and Phase Contrast MRI. While with the relatively new technique, MR Elastography, mechanical characteristics of (soft) tissues can be directly determined. Each of these three techniques will be briefly discussed in the following sections.

1.2.1 MR Tagging

MR tissue tagging with dynamic MR imaging is a rapidly developing technique for the quantitative, non-invasive evaluation of displacement within muscle with a high spatial and temporal resolution [24]. The technique works as follows: Over a period of milliseconds the magnetization of tissue is periodically modulated with a grid pattern, thus forming tags. If the tissue moves, the magnetization tag will move along with it, directly revealing the displacement of the tagged region in the subsequent image, see figure 1.1 [01, 02, 30, 36]. Mathematical techniques can then be used to reconstruct a 3-dimensional deformity from tag positions on MR images [24]. Also, detailed motion of the tissue can be deduced by analyzing the deformation of taglines found within these images [34].

Figure 1.1: Coronal in vivo MR tagging images of a mouse hind limb leg (a) in rest and (b) during contraction by stimulation of the sciatic nerve. Reproduced from [34]

Diffusion Tensor Imaging (DTI) can be combined with MR tagging to determine fiber orientation during contraction or deformation. DTI measures the direction in which water diffused within the tissue. The path of least resistance is for water to diffuse in the direction of the muscle fibers (see figure 1.2). This is an interesting option as muscle damage might lead to a localized decrease in the diffusion anisotropy. The muscle fiber orientation could provide valuable input for mathematical finite element models of skeletal muscle mechanics [34].
1.2.2 Phase Contrast MRI

Phase Contrast (PC) MRI is a method often used to study flow (e.g. in the circulatory system). It uses differences in signal amplitude to differentiate between stationary and flowing spins (spin is the precessing movement of unpaired protons about their axis). MR data have both amplitude and phase. Spins moving along a gradient accumulate a phase shift relative to stationary tissue. This phase shift gives a good contrast between moving and stationary tissue. PC MRI provides one anatomical image and three velocity images (x, y, and z directions) for each time frame of the motion cycle. The velocity images can be integrated to determine the deformation and strains of tissue in vivo. PC MRI might be more accurate than tagged MRI, but is more sensitive to errors from magnetic susceptibility gradients, higher order motions, and has a limited dynamic range. Long scan times are needed: PC MRI requires multiple cycles of motion; typically 60-120 repetitions are needed to acquire composite images representing one motion cycle. The requirement of many motion cycles creates a set of problems. One of which is the fact that the quality of the images degrades dramatically if the motion cycles are not repeated accurately [25, 27, 31, a].

1.2.3 MR Elastography

Magnetic Resonance Elastography (MRE) is a relatively new diagnostic method for detecting changes in the mechanical properties of tissue. MRE can be applied to a variety of tissues, but has so far mainly been successful in detecting tumors within soft tissues (e.g. the breast or the brain) [18, 34]. Little is known about the elastic properties of in vivo (skeletal) muscle, present MRE studies are therefore mainly focused on determining the mechanical properties of healthy muscle [10].

MRE works by applying mechanical vibration to the skin, superficial to the muscle(s) of interest. This vibration creates spherical waves (i.e. shear and compression waves) within the muscle. MRE images only the shear component, which in muscle has a wavelength on the order of centimeters. The shear waves seem to follow the muscle fibers from the point of application. The measured wavelength is dependent on the passive tension (from stretching) and the active tension (from contraction) [04, 10, 16]. See figure 1.3 for an example of an MRE application.
Figure 1.3: (a) Schematic diagram of the set-up for the MRE measurements of the biceps brachii muscle under loading conditions. (b) Normal axial MR image of the arm. (c) MRE wave image at a single phase in the coronal slice indicated with the rectangle in (b). Adapted from [10, 34]

The current problem with MRE is that the shear stiffness modulus and the tension in the muscle must be calculated from the wavelength. This requires that a constitutive model of the elastic properties be assumed. Work to date has assumed that muscle is a bundle of linearly elastic fibers within a viscous medium.

The main issue is that muscle is an anisotropic material. This issue might however be met assuming that it is transversely orthotropic (i.e. there is one stiffness along the bundle of fibers and a different stiffness transverse to the bundle of fibers). This is the model that is currently assumed. Whether this assumption leads to errors, and what the magnitude of said errors might be, is currently unknown (Jenkyn, 2003)

Once the MRE method is perfected with respect to the determination of the properties of muscle tissue, it could provide the material parameters needed for finite element modeling of muscle deformation.
2 Muscle damage

By the nature of their position in the body, skeletal muscles are frequently subjected to physical trauma [19]. Muscle tissue will be damaged if the magnitude of the applied load is high enough or the duration is long enough, e.g. after (severe) crush injuries, or after lying on a hard surface for extended periods of time [19]. Figure 2.1 shows the relation between pressure magnitude and duration of load.

![Figure 2.1: Risk curves with regard to tissue damage. Time/pressure combinations above the curve result in tissue breakdown. Adapted from [33]](image)

The mechanical properties of skeletal muscle will change as a result of damage. Damage is initiated locally, so data on local deformation is essential for understanding the cause of muscle damage. Muscle damage and adaptation are initially local phenomena at the level of individual cells (see figure 2.2). To find a damage threshold for skeletal muscle it is necessary to know how external loads are transferred to local loads within the tissue. In order to study local muscle loading, numerical muscle models have been developed. To simulate realistic 3D muscle deformation, these models should have a realistic 3D geometry, since deformation in transverse direction is not negligible. Such a model, combined with experimental results, offers a solid tool to improve insights in muscle mechanics of damage [13, 20, 33, f, g].

![Figure 2.2: (a) Longitudinal histological section of muscle showing the typical cross-striated appearance of skeletal muscle (arrowhead), a loss of cross-striation of muscle fibers in the damaged area (small arrow) and the infiltration of mononuclear cells (large arrow). (b) Detection of the damaged area within part of a slice. Adapted from [05]](image)
Previous work has mainly focused on the determination of muscle damage in the form of pressure sores. There, MRI was used to determine muscle damage after prolonged transverse loading. Histological data obtained after testing was compared to data obtained through MRI. It was found that the location of higher signal intensity in MR is in agreement with the location of muscle damage assessed in the histological examination; see figure 2.3 [05, 06, 34]

![Figure 2.3: Damage in transverse histological slices (bottom) and MR images in the center plane of the indentor. Adapted from [05, 33]]

Muscle damage was defined as loss of cross-striation and infiltration of mononuclear cells. Evidence of this trauma is visible 24h after loading occurred (figure 2.2). Kosiak (1961) found that intense pressures of short duration are as injurious to tissues as low pressures applied for longer periods (see figure 2.1) [33]. Muscle damage after impact, short duration – high magnitude loading, is likely of a different type than that occurring after prolonged periods of loading at lower load magnitude.

The equipment used in the current study by Stekelenburg [33, g] can be adapted for use in the HUMOS II project; it makes use of a loading apparatus to apply pressure to soft tissues in a rat model while inside a MR-facility (see section 3.1). With this setup one could detect in vivo the early stages of tissue damage as a result of the mechanical load. The muscle used in this project is the tibialis anterior (TA). The setup is similar to that used in the study by Bosboom [05], with the exception that the testing here can be done inside the MR environment.
3 Experimental - Numerical Work

A common method to determine material mechanical characteristics is to subject specially machined samples to tensile loading. This uniaxial strain test makes use of a well-defined basic shape; the sample is designed in such a way that loading should lead to a homogeneous strain distribution in the central region. However, standard ways for quantitative determination of material parameters result in insoluble problems when applied to complex solids [17]. When performing a uniaxial strain test it is assumed that the central part of the sample undergoes uniaxial loading (figure 3.1a) and that its properties are representative for the material as a whole [17]. While these are valid assumptions for a homogeneous material, biological material is not homogeneous. For complex biological materials, standard testing often fails to give satisfactory results. Extreme anisotropy produces inhomogeneous stress and strain fields (figure 3.1b), while standard testing requires these to be homogeneous [32]

![Figure 3.1: Strain distribution in a homogeneous (a) and complex / biological (b) sample](image)

Because biological material is inhomogeneous, manufacturing samples will result in destruction of the internal structural coherence; only part of the fibers will be loaded in a uniaxial strain test. Furthermore, in preparing the sample for tensile testing, the material needs to be cut to the desired shape. In case of biological material, this will damage and alter its structure completely, so that test results no longer represent the material under consideration. [17, 32]

When characterizing complex materials better results are obtained when the strain distribution in the entire sample is recorded (Peters, 1987). Using a mixed numerical-experimental method, the deformation data of the entire sample is measured [17, 32]. This data can be obtained in a variety of ways (see chapter 1).

The mixed experimental-numerical method was developed specifically to characterize complex materials. With the experimental-numerical method there is more freedom in the design of experiments, and for the characterization of complex materials. The key point for material characterization is the combination of displacement field measurement, finite element modeling (FEM) and parameter estimation. Using FEM and an adequate constitutive model the experimentally determined deformation can be mimicked and, in doing so, the model's parameters can be determined [17, 23, 32]

In this chapter the experimental and numerical aspects will be briefly touched upon.
3.1 Experimental Aspects

In vitro studies have been done on excised muscle tissue. For the results of such research to be representative of in vivo conditions, care has to be taken to preserve the in vivo muscle length, prevent dehydration and degradation of the tissue. Deformation can be tracked by using markers glued to the muscle surface in combination with a camera setup (see section 1.1) [20, 35] and tissue damage can be determined by histological or MRI assessment. However, excised muscle tissue no longer has a functioning neurovascular system. Due to this the damage mechanics will be different than in living tissue [15]. An improvement was made by only partially excising the muscle while keeping the neurovascular system intact [05, 06, 07]. However, external tracking, as previously discussed, has some drawbacks. Externally measured strains are not representative of internal strains. Internal deformation is best visualized using MRI. MRI has been successfully used to study deformation and the onset and location of damage in muscle tissue [05, 20]. Figure 2.2a-b shows the experimental setup and visualization used by Bosboom [05]. Figure 2.2c shows results of a test similar to the one shown in figure 2.2a-b, but modified for use inside an MR environment.

Figure 2.2: (a) Loaded region of rat leg, (b) cross section of rat's hind limb during loading showing the compression of the tibialis anterior (TA) muscle between indentor and tibia, (c) Coronal ex vivo MR image of a rat hind limb with water filled indentor pressed into the tibialis anterior muscle. (a) and (b) adapted from [05], (c) adapted from [34]

Various experimental setups have been employed to apply a load to muscle tissue. Both longitudinal stretching [20] and transverse compression [05, 06, 35, g] apparatus has been used. Stekelenburg is currently developing a set-up that can be used for vivo MRI assessment of tissue damage. This work also uses the rat as animal model and focuses on the tibialis anterior (TA) muscle. Examples of the experimental setup can be seen in figure 3.3. In the present study, where short-duration, high magnitude loading (impact) situations are of interest, the experimental setup (to be) used by Stekelenburg [33, g] could be adapted for use.

Figure 3.3: experimental setup used by Stekelenburg. (a) Rat limb is fixated using a plaster cast. (b) Early MR coil and indentor design. (c) Rat limb clamped inside experimental setup; hole cut in plaster to expose the tibialis anterior (TA) muscle. Courtesy of A. Stekelenburg.
3.2 Numerical Aspects

As mentioned previously, to determine the mechanical parameters of muscle tissue, it is necessary to pair the experimental data with a suitable finite element model, in combination with an adequate constitutive model. Geometry and (micro-) structure of the FEM model will have to resemble that of the real muscle.

Numerous studies have been done on the numerical representation of muscle behavior. In literature, Hill type models are often chosen for the active stress [11]. Later work also focuses on different variants of models based on the theory of Huxley (1957) [13, 20]. These latter models give good results for relatively slow phenomena, compared to experimental data [20]. Another model, used to describe the passive muscle behavior, is the incompressible viscoelastic Ogden model (Ogden, 1982). The highly nonlinear, viscoelastic behavior of muscle can be very well described using this model [05, 06].

An important tool in solving the boundary value problem is finite element modeling (FEM) software. Here the geometry of the sample is approximated by a simpler structure, composed of a finite number of elements, thus reducing computational time. An example of such a mesh is shown in figure 3.4, where a section of TA muscle with a layer of skin and the indentor are modeled.

![Figure 3.4: 3D finite element mesh of a section of muscle, skin and indentor. Arrows indicate suppressed displacements at the interface with tibia and membrana interossea. Adapted from [05]](image)

Once the mesh has been built, and an appropriate constitutive material model has been chosen, the mechanical parameters can be determined. This is usually done by means of parameter estimation, often preceded by a sensitivity analysis. Parameter estimation works as follows: An initial estimation is given and during the process the estimated parameter is continually improved by comparing it to the experimental data. The estimation is corrected by inputting the difference between the calculated data and the measurement into an iterative scheme. This process will continue a fixed number of steps or until the difference between estimation and measurement is within a certain limit [08, 09, 12,].

It is not always necessary to run through this entire iterative scheme. On occasion manual variation of the parameters can be sufficient to determine which parameters have most influence on the mechanical behavior, and consequently vary them in such a way that the measured behavior is approached in the model.

A description of the methods available in parameter estimation can for example be found in Gelb (1999) [12]. An example of an iterative scheme is Parfit, written and first used by Meeuwissen [22] and later by Thomassen and Bosboom as well [05, 06, 35].
4 Discussion / Conclusions

As mentioned in section 1.1, optical tracking methods should not be used to evaluate muscle deformation. In order for them to yield useful information, the muscle needs to be excised which is unacceptable as the tissue should remain alive and the neurovascular system intact [06]. Even if all conditions were ideal, the superficial strains measured by optical camera tracking, be it 2D or 3D, are not a good measure for deep strains.

Of the Magnetic Resonance techniques discussed, MR Tagging seems the best candidate. First of all, there is a fair amount of experience using this technique in combination with muscle/indentor studies at the Eindhoven University of Technology. It can be used to measure contraction and deformation of skeletal muscle [01]. Furthermore, if DTI (Diffusion Tensor Imaging) is combined with MR tagging, fiber orientation can be determined during contraction or deformation [34].

The other MR techniques discussed (PC-MRI, MRE) are not unusable, but the disadvantages mentioned in section 1.2.2 and 1.2.3 are such that it is thought better to not use them in the present study. Of these two methods Magnetic Resonance Elastography seems a promising new method, but due to the assumptions made regarding muscle material properties, it is best left for a future study.

Recent decubitus studies have made use of MR to track deformation in muscle tissue under loading [05, 06, 20, g]. Work done in these studies might be adapted to this research. Main difference is duration and magnitude of applied load. Assessment of muscle damage might be done as described in [05], where MRI damage assessment and histological examination were compared and found to be in good agreement. Perhaps initially histological examination could be performed in addition to MRI assessment, to verify that they are in agreement. If this is found to be the case, MRI damage assessment can be used in favor of histological examination.

For reasons described in the previous chapter (section 3.1), it is considered unwise to do in vitro experiments, especially if tissue damage is to be studied. Furthermore, previous study showed damage to manifest itself 24h after loading. The neurovascular supply is important in the process of damage and repair; damaged muscle releases intracellular components into the blood stream, and the blood carries nutrients and cells needed for the repair. If the blood supply is removed, the damage and repair mechanisms are altered as well [07, 15, 19]

The modeling tools to be used will be Sepran, as this program allows the greatest amount of freedom in modeling (section 3.2). A drawback is that it requires a reasonable amount of programming skill and that it is difficult to model contact between two bodies. An alternative would be to use MARC/Mentat in combination with Parfit. This combination has been used in previous research [05, 22, 23, 35]. Ultimately the modeling freedom of Sepran is thought to be of greater value than the ease of use with the Marc software.

A benefit of using an indentor setup in the experiments, instead of one where the entire muscle is compressed, is that only a section of the muscle needs to be modeled (see figure 3.4), reducing the mesh size and amount of time needed to create it, and also reducing the computation time.

The exact constitutive model to be used has yet to be decided upon, but it should build/expand on work done by Gielen, Bosboom and Maenhout [05, 13, 20]. It should improve on the Ogden model and/or the Huxley models used in these studies.
## Proposed time table

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<th>Date Range</th>
<th>Task Description</th>
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<tr>
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<td>Nov - Jan</td>
<td>Literature review and report</td>
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<td>2</td>
<td>Feb - Mar</td>
<td>Start up of experimental and numerical work;</td>
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<td>Get Sepran software operational, familiarize with software, simple FEM modeling;</td>
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<td>Work on experimental setup; familiarize with MRI equipment, lab animals</td>
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<td>3</td>
<td>Apr - May</td>
<td>Pilot experiments (in vitro?); Start up modeling of TA muscle in Sepran – or</td>
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<td>Jun - Jul</td>
<td>Actual in vivo experiments; Finalize numerical model; fit to experimental data.</td>
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<td>Aug - Sept</td>
<td>Work on and finish final report; Finish up experiments; Work out final details</td>
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Lay Language version of paper MO-D-518-7
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Bosboom E.M.H., Bouten C.V.C., Oomens C.W.J., et al, "High res. MRI to assess skeletal muscle damage after compressive loading" (see also Bosboom PhD Thesis)

Bosboom M., Thomassen S., Oomens C., Bouten C., Baaijens F., "Transverse mechanical properties of skeletal muscle" (see also Bosboom PhD Thesis)


Maenhout M., Drost M., Oomens C., Baaijens F., "Strain fields within contracting skeletal muscle" (see also Maenhout PhD Thesis)

Stekelenburg A., Oomens C.W.J., Bouten C.V.C., Bader D.L., Nicolay K., "Magnetic Resonance Techniques to Study Damage Evolution in Muscle"

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