ROBOTICS AND MECHATRONICS

PERSONALIZED PREDICTION OF KNEE LIGAMENTS MECHANICAL PROPERTIES USING MR IMAGES

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Acknowledgment

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Abstract

The health status assessment of the knee ligaments is currently performed via qualitative observation of MR images. Knowing quantitatively to which extent the ligaments can be mechanically stressed before an injury occurs is only possible after invasively collecting a sample of the ligament's tissue. Computational models for personalized knee joint surgery pre-planning are a possible alternative and they rely on the study and observation of the main tibiofemoral ligaments. **Objectives** - Magnetic resonance imaging (MRI) of the knee is the standard-of-care imaging modality to evaluate knee disorders, and more musculoskeletal (MSK) MRI examinations are performed on the knee than on any other region of the body and for this reason this study focuses mainly on researching into finding a model capable of predicting knee ligaments mechanical properties from MR images. A recent study conducted by Naghibi et al. [1] explored the potential role of quantitative MRI and dimensional properties, in characterizing the mechanical properties of the main tibiofemoral ligaments. After MR scanning of cadaveric legs, all the main tibiofemoral bone-ligaments-bone specimens were tested in vitro to measure their stiffness and rupture force. The study revealed the potentials of using quantitative MR parameters combined with specimen volume to estimate the essential mechanical properties of all main tibiofemoral ligaments required for subject-specific computational modelling of the human knee joint. This study aims to continue the investigation conducted exploring the chances of creating a model that proves correlation between MR images data and mechanical properties. **Methodology –** Previous studies observed promising results while deriving average values (like cross sectional area and qualitative MR image parameters) of the whole ligament to produce a correlative model between MR images and mechanical properties. In this study we explore the chance of creating a model that correlate regional characteristics to mechanical properties. The assumption is that the knee ligaments, like most biological tissues, have different characteristics regionally. For this reason, the MR Images composing the dataset are segmented and processed specifically to partition each ligament into smaller portions. By doing so there is the added value of a increasing the size of the dataset. From each of these sub-volumes the following parameters are extracted: volume, cross-sectional area and average MR value ($T_{1\rho}$). These parameters are subsequently used together with the mechanical parameters measured during the tensile test by Naghibi et al. [1] to train a linear regression model. To evaluate the results, the output of the created model is compared with the output of the model created by Naghibi et al. **Results** - The results collected in this study display a little correlation on the training set and no correlation on the test set. The inclusion of the ligament type in the model produced marginally better results. **Discussion** - From the results of this study, it can be inferred that, in agreement with the literature, the volume (without partition) is the parameter with the highest influence on the correlation between MR images and mechanical properties. Moreover, it has been proven that, in agreement with the literature, the distinction between ligament type improves the correlation. It is not possible yet to conclude whether there is a correlation between MR images data and mechanical properties.

Commentato [NBH(1]: Quantitative MR images (T1-rho, …)

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1. Introduction

The knee, as the most weight-bearing joint in the human body, is also the most prone to injuries. This study focuses on the knee ligaments' health assessment. Technological advancement of magnetic resonance imaging (MRI) makes it the most precise method of assessing the knee joint soft tissues' health condition. Availability of more powerful magnets and other technical upgrades improved the result consistency as well as the imaging capability extending it to increasingly smaller anatomical details. Evaluation with MRI is currently a gold standard for a comprehensive assessment of the knee joint soft tissues making it also extensively adopted.

Currently computational models for personalized knee joint surgery pre-planning relies on the study and observation of the main tibiofemoral ligaments and in-vivo ligament measurement applications are limited by the non-applicable standard techniques of assessing the mechanical stiffness and rupture force of the above-mentioned tissues that are commonly performed on cadavers sampled tissues.

The currently available quantitative measurement techniques are highly invasive, they must be done under local anaesthesia, and they are typically performed on patients who are undergoing a surgical procedure. Many of these measurement techniques are limited to isolated regions of the ligament, and not the whole structure. The current strain measurement techniques mostly consist of devices that attach directly to the tissue (e.g. Differential Variable Reluctance Transducer). Force measurement techniques include the Buckle transducer, fibre optic sensors, and other force probes that can be implanted in or around the mid-substance of the tissue [3]. Knowledge about quantitative mechanical properties of the knee ligaments obtained using a non-invasive method can provide a determining insight in whether a surgery has been successful and whether a ligament is capable of sustaining more than physiological mechanical tension (hence allow to: walk, ascend stairs, descend stairs, run, etc…).

It has been demonstrated previously that relying on the values from literature for ligament stiffness as an attempt to obviate the invasive assessment methods can lead to inaccurate outcomes due to the wide range of reported properties [2]. This limits the achievement of non-invasive approaches for properties estimation based on knee laxity in clinical implementation. For such reason, it's believed that the use of computational models has the capability of supporting the physician in the surgery pre-planning maintaining a non-invasive approach. By assigning personalized mechanical properties for knee ligaments in computational models, errors in model predictions caused by large inter-subject variability can be reduced [2].

A recent study explored the potential use of quantitative MRI and dimensional properties, in characterizing the mechanical properties of the main tibiofemoral ligaments [1]. After MR scanning of cadaveric legs, all the main tibiofemoral bone-ligaments-bone specimens were tested in vitro to measure their stiffness and rupture force. Digital image correlation technique was implemented to check the strain behaviour of the specimen and rupture region and to assure the fixation of the ligament bony block during the test. Linear mixed statistical models for repeated measures were used to examine the association of MRI parameters and dimensional measurements with the mechanical properties (stiffness and rupture force). The study revealed the potentials of using quantitative MR parameters combined with specimen volume to estimate the essential mechanical properties of all main tibiofemoral ligaments required for subject-specific computational modelling of the human knee joint.

The above-mentioned study showed clues towards promising results by adopting parameters obtained averaging the value throughout the whole ligament volume and explored the advantages of accounting for different quantitative MR image parameters ($T_1\rho, T_2, T_2^*$) and ligament types.

Commentato [NBH(2]: Quantitative MR images (T1-rho, …)

In this study, we explore the improvements that can be brought to the computational model and the image processing algorithms proposed in the literature by identifying the weaknesses and strengths of the methods adopted previously and offering new solutions. The ligament is investigated as non-uniaxial material composed of fibres bundles that cause region-specific mechanical behaviours.

This project aims to design, develop and validate an approach to estimate the main four knee ligaments mechanical properties improving the magnetic resonance imaging analysis intended to identify pathological structures answering the question:

"given the results obtained in the literature and the material available is it possible to observe significant correlation between MR images and mechanical data and predict the rupture region by analysing regional characteristics of the ligament?"

1.2 Goals

The aim of this study is to research a method that non-invasively and accurately estimates quantitatively the mechanical properties of the four main knee ligaments from MR images. More specifically the focus is on assessing whether ligament region specific characteristics can improve the linear correlation model relating MR images and mechanical properties presented in the study of Naghibi et al. [1].

The objectives of this study are summarized as follows:

1. Analysis of MR images and datasets and identification of parameters that fit the task of estimating the mechanical properties of soft tissues.
2. Assessment of the influence of the identified parameters (from point 1) on improving the prediction model
3. Validation of the designed model(s) and algorithm on a test set

1.3 Anatomical background

The knee, identified as the joint connecting the femur and the tibia, has the two main functionalities of flexion and extension of the leg. It works mainly as a complex hinge that allows, in healthy patients, to variate the angle between two of the longest bones of the body from full extension at 0^o to full flexion at 155^o enabling more than just walking and climbing stairs [3]. A closer inspection reveals that the knee is actually capable of a total of 6 degrees of freedom: three translational and three rotational movements (Fig. 1). Literature finds agreement in stating that the overall stability of the joint is to be identified in the combined effect of active stability of the muscles and passive stability of the ligaments [4]. It is therefore straight forward to conclude that the rupture of one of the ligaments implies severe instability of the joint that compromise its natural function.

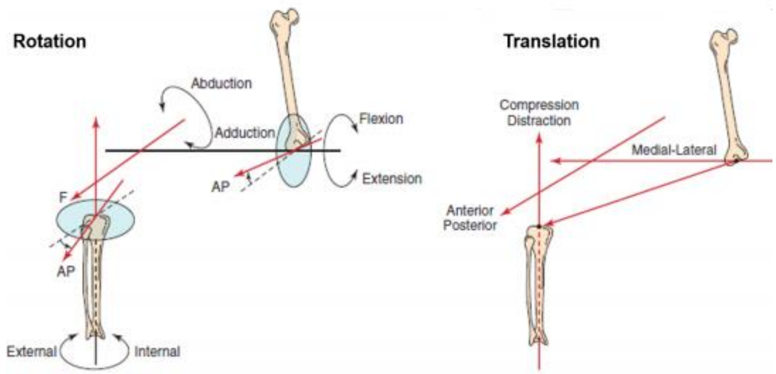

Fig. 1 Rotational and translational capability of the knee joint. [4]

1.4 State of the art

The current method adopted for the evaluation of the knee ligament' health condition as well as pre- and post- surgery evaluation is via qualitative observation of the MR images. Making use of different angle view an orthopaedic surgeon can identify anomalies in the soft tissues of the knee.

When it comes to MRI based computational model very little has been researched up to this point. To the best of authors knowledge there has been only one previous study that explored the correlation of single volumetric MR images with corresponding mechanical properties. Prior to that, Biercevicz et al. attempted to correlate graft volume and signal intensity with a single legged hop test which is non-invasive method to assess the functionality of the lower limbs.

Naghibi et al. [1] performed the only study that accounts for the complexity of collecting adequately the data up to this point and it has set the basis that make this study possible.

In the above-mentioned study, quantitative MR images ($T_1\rho, T_2, T_2^*$) have been acquired on the lower limbs of six fresh-frozen human cadavers with a mean age of 78±11 years making sure to select those without any obvious signs of injuries in the lower extremity. Subsequently, the legs have been prepared for the extraction of the ligaments. Then the ligaments, complete of the insertion site with the femoral and tibial bone, have been mechanically tested. From the MR images, parameters such as the volume and the average cross-sectional area have been manually extracted together with the average quantitative MR value. The MR images parameters and the mechanical properties have been used to build a linear regression model (Fig.2). The results highlighted the presence of linear correlation with an appreciable margin of improvement in relation to ligament type parameterization and the strong influence of the ligament volume on the quality of the result. It is to be noticed that the main focus of the above-mentioned study was of biomechanical interest, hence primarily focused on the extraction and observation of the mechanical data from the ligament as well as the acquisition of MR and ultrasound images, differently from the current study that focuses more on the statistical model creation and assessment.

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Commentato [NBH(4]: Quantitative MR values

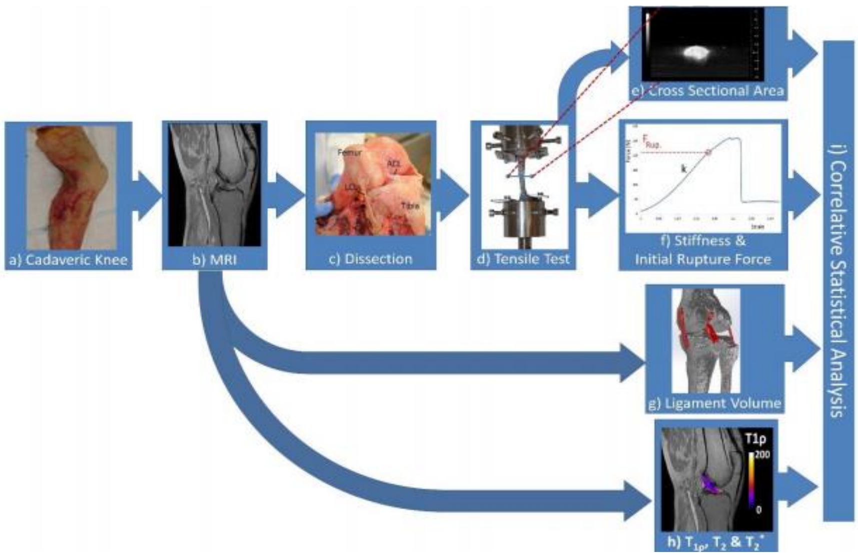

Fig. 2 Schematic representation of the data acquisition procedure performed by Naghibi et al. [1]

1.5 Approach

This section summarizes the structure of the study, aiming to provide a clear overview of the research and facilitate the understanding of the approach.
Refer to Fig. 2 for a graphical representation of the structure of this study.
Hereby are reported the summarized steps that compose the algorithm created and adopted in the current study:

- The dataset available to perform the research are composed by a set of MR images of the 6 cadavers' legs (for a total of 24 sets) and the respective mechanical data.
- The MR images segmentation is required to separate the ligament foreground from the background. Once segmented, the images can be piled together to create the ligament 3D model (accurate to the best of the image resolution and manual accuracy in performing the segmentation).

- Each ligament's volume is further processed to divide the volume in smaller sub-regions and extract from each of these: volume, cross sectional area and average MR intensity value.
- These three values, from each region, are subsequently used together with the respective ligament's mechanical properties to train a standard multiple linear regression model.
- Multiple models are created with the aim of investigating which parameters positively influence the correlation outcome.
- The correlation results are compared with those reported in the study performed by Naghibi et al. [1], who conducted a study using a different approach however adopting the same dataset.

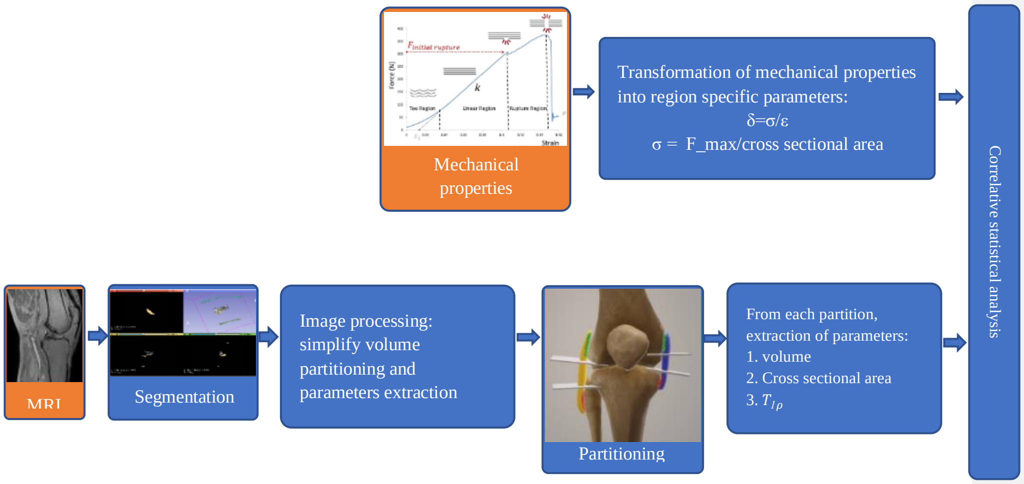

Fig. 3 Project schematic. This figure shows the sequence of steps that allow the extraction and transformation of the data necessary to the correlative statistical analysis. Once the ligament is partitioned the parameters for the analytical model can be easily extracted like described in paragraph 2.5. The blocks with an orange background are the image data and mechanical data that are shared with Naghibi et al [1].

2. Materials and methods

In this chapter, the MR imaging section (2.1) and the mechanical stress test section (2.2) are a description of how the data that have been collected by Naghibi et al. [1] since this study is brought on using the same image and mechanical data. Such decision is made based on the difficulty of acquiring new data on cadavers that have never been analysed before and provided the full access to the above mentioned already existing datasets.

2.1 MR Imaging

Hereby are reported more details regarding the method of image acquisition previously adopted by Naghibi et al. [1] since the same dataset is used in the current study. In this section only the details that have relevance for carrying out this study will be described.

The legs have been placed in lateral position inside a 3T Philips Ingenia MRI scanner (Philips Healthcare, Best, The Netherlands) in two positions: in full extension and also at a 30° angle. This has been done to guarantee the tension in all the ligaments as it is known that the MRI signal intensity of ligaments is influenced by the tension in the ligaments [6] and the magic angle effect [7].

Magnetic resonance (MR) imaging signal intensity is primarily determined by intrinsic factors (relaxation time, proton density, flow, susceptibility effects) and extrinsic parameters (repetition time [TR], echo time [TE], and flip angle). The magic angle effect occurs in all collagen-rich structures and is the cause of a modulation of dipolar interaction correlated to the orientation of the collagen fibres with the main magnetic field. This artifact affects the relaxation times making them angle dependent. This results in alterations in signal intensity according to the orientation of collagen fibres and the magnetic field. Statistically T_2^* is the quantitative MR parameter that is affected the most by the magic angle effect, it is however possible to include the parameters $T_1\rho, T_2$ to acquire complementary knowledge to compensate for the magic angle effect. For the reason just explained the acquisition of all three quantitative MRI parameters is performed to guarantee the most comprehensive knowledge about the ligament from an image point of view.

At each position the following sequences were acquired:

- proton density-weighted (3D Turbo Spin Echo, voxel size = 0.31 × 0.31 × 0.52 mm^3, matrix size = 720 × 720 × 250, TR = 1000 ms, TE = 41 ms, NSA = 2, acquisition time = 6 min 40 s);

- proton density-weighted with fat suppression (3D Turbo Spin Echo, SPAIR fat suppression, voxel size = 0.31 × 0.31 × 0.63 mm^3, matrix size = 720 × 720 × 206, TR = 1300 ms, TE = 153 ms, NSA = 2, acquisition time = 12 min 35 s);

- T1ρ map (B0 and B1 compensated spin lock pre-pulse, 3D gradient echo readout, voxel size = 0.6 × 0.6 × 2 mm^3, matrix size = 320 × 320 × 131, TR = 3.6 ms, TE = 2 ms, flip angle = 15°, spin lock time = 1, 5, 10, 20, 30, 40 ms, spin lock frequency = 500 Hz);

- T2* (3D gradient echo, voxel size = 0.6 × 0.6 × 1 mm^3, matrix size = 320 × 320 × 131 , TR = 104 ms, TE = 4.1, 8.1, 12.1, 16.1, 20.1, 24.1, 28.1, 32.1, 36.1, 40.1, 44.1, 48.1, 52.1, 56.1, 60.1, 64.1 ms, flip angle = 15°);

- T2 (multislice multiecho spin echo, voxel size = 0.7 × 0.7 × 1 mm^3, matrix size = 320 × 320 × 131, TR = 7000 ms, TE = 12.1, 18.2, 24.2, 30.3, 36.3, 42.4, 48.4, 54.5, 60.5, 66.6, 72.6, 78.7, 84.8ms).

2.2 Mechanical stress test

In this section are reported more details regarding how the ligaments' mechanical properties have been acquired by Naghibi et al. [1]. Hereby can be found exclusively the details that have a meaningful impact on the carrying out of this study.

After completion of the MRI scans, the six knees were dissected by an orthopaedic surgeon to extract the 4 main knee ligaments (ACL, PCL, MCL, and LCL), preserving the proximal and distal bone blocks (for a total of 24 specimens in total, 4 ligaments per 6 legs from 6 different cadavers).

Each ligament was subject to mechanical test trying as accurately as possible to recreate the physiological conditions. Force-strain curves for each ligament were extracted as shown for a single specimen in Figure 2. The stiffness (k) was calculated for each ligament based on the model described by Blankevoort and Huiskes [12] for non-linear mechanical properties as follows:

$$f(\varepsilon) = 0 \quad \text{for } \varepsilon < 0$$

$$f(\varepsilon) = k\,\frac{1}{4}\varepsilon^2/\varepsilon_l \quad \text{for } 0 \leq \varepsilon \leq 2\varepsilon_l$$

$$f(\varepsilon) = k(\varepsilon - \varepsilon_l) \quad \text{for } \varepsilon > 2\varepsilon_l$$

Where f is the tensile force in a line element, k is the ligament stiffness, ε is the strain in the ligament and ε_l is a strain constant.

The initial rupture force for each specimen was also extracted from the force-strain curve for instance indicated in Fig. 4 in a representative specimen. The region of rupture in the specimen was defined from digital image correlation and checked using ultrasound data.

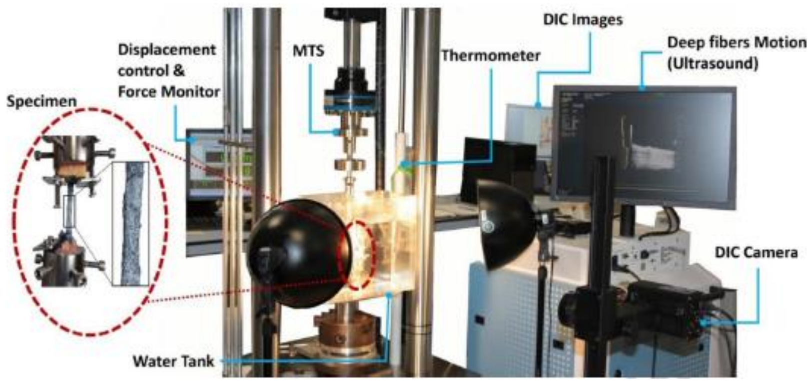

Fig. 5 Mechanical stress test set up used to extract the mechanical properties of the ligaments [1].

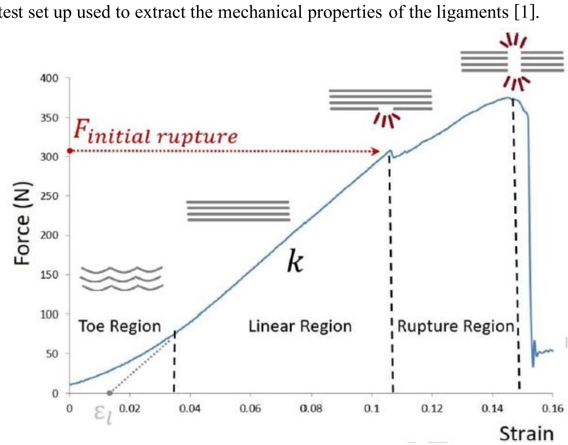

Fig. 4 A force-strain curve example of an LCL specimen with the distinction between toe region, linear region, partial rupture and total rupture region [1].

2.3 Image processing

Image processing has the important role of allowing the connection between image parameters and mechanical properties. The fundamental aspect of this part of the algorithm is to exhaustively analyse the MRI acquired images to precisely extract the information that can have relevance in determining a correlation with real-life mechanical properties. The extracted parameters are the volume, the cross-sectional area and the MR intensity value ($T_{1\rho}, T_2, T_2^*$). The focus was specifically on those MR image derivable characteristics that are considered to have a close impact on the mechanical properties of the ligaments.

Together with the above-mentioned parameters one of the points of innovation of this study is the research in regional specific characteristics and for such reason, image processing is also used to define how the ligament is partitioned for further analysis. Together with the intention of prioritizing the identification of the rupture region the volume partitioning and region specificity help towards the very limited number of samples available.

2.4 Ligament segmentation and partitioning

A necessary step to begin working on the images is the segmentation of the ligaments. A first segmentation has been performed on the entire dataset by an expert, this allowed for easier and accurate distinction between the ligaments and the other tissues. An additional segmentation has been done afterwards using the software 3D Slicer 4.10.2 [18] to facilitate the automatic distinction between different ligaments in the same volume and also between ligaments in contact with each other (ACL and PCL, without manual segmentation at the current state of the art the two ligament would appear as an ‘X’ shaped body without clear distinction between the two separate ligaments). The segmentation tool is also used to identify the region of contact of the ligaments and the bones which are characterised by irregular shapes with great variability.

As reported in literature the rupture region, in patients without previous lower limbs injuries, variates mainly depending on the age of the patient. The regions of contact with the bones are frequently the point of rupture in older patients whilst in younger ones it's more frequent to observe the rupture in an intermediate position along the ligament principal axis [2]. Assessed the propensity to rupture, it's considered particularly important to identify adequately the region of contact of the ligament with the bone. For this reason, such regions are segmented manually due to the extreme variability in shape and position that depend on subject and ligament type. An additional advantage of doing so is that the ligament orientation can be preserved during more abstract parts of the algorithm allowing the distinction between femoral and tibial extremity.

Each ligament is divided into 5 three-dimensional regions, two of which correspond to the region of contact of the ligament with the bone and the other three instead correspond to the remaining volume divided into three sections along the local central axis. The local central axis is obtained via skeletonization of the ligament volume and deletion of the secondary branches. Skeletonization is defined as a process for reducing foreground regions in a binary image to a skeletal remnant that largely preserves the extent and connectivity of the original region while throwing away most of the original foreground pixels. The result of it, in this case, is a line of voxels at the centre of the ligament volume along the length (Fig.5 central). Secondary branches are the result of smaller details mostly on the ligament's surface and they are a common trait of this operation.
These secondary branches function as noise when trying to identify the central local axis. They are identified by listing all the voxels that have only one confining

voxel as an “end” and voxels that have three or more confining voxels as a “joint”. Identifying the main axis is a matter of comparing the direction and the length of the segments comprised between joints and ends. The orientation of each segment is compared with the main direction of distribution of the voxels obtained via PCA. The correct segments are found by comparing their length and orientation with a threshold (Fig. 5).

Knowing the local central axis strongly simplifies the method of partitioning of the volume independently from the three-dimensional shape of the ligament allowing to automate the remaining processes of parameter extraction. Starting from the local central axis, two points at one third and two thirds of the length define where the volume of the ligament is being cut by planes perpendicular to the central axis (Fig. 6).

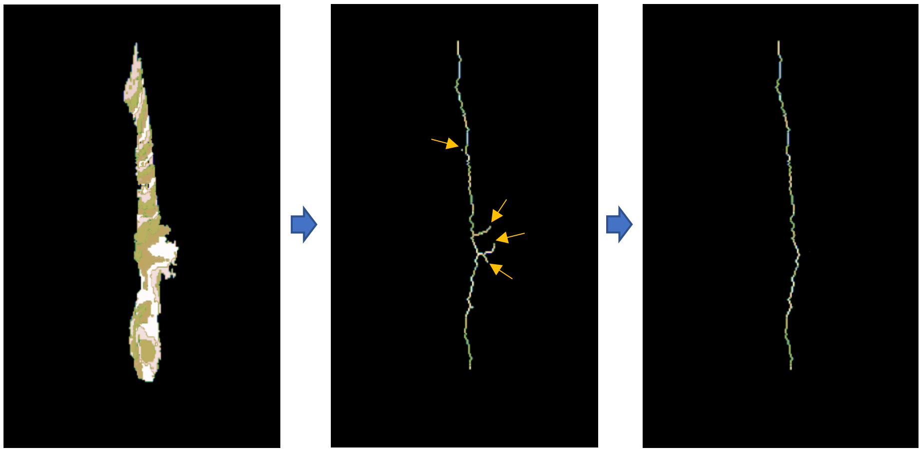

Fig. 5 (left) 3D model of a ligament (LCL) obtained via segmentation. (centre) Skeletonization of the same ligament in the right picture and identification of secondary branches. (right) The effect of the secondary branches deletion algorithm.

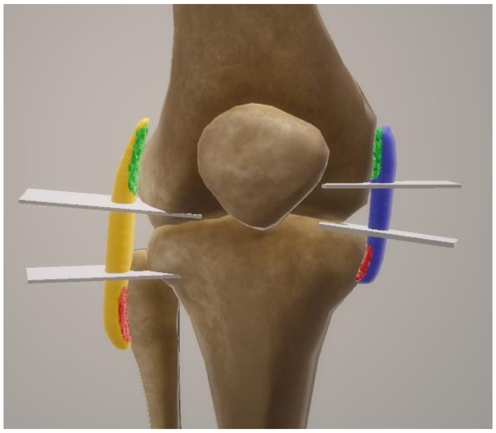

Fig. 6 Drawing representative of how the ligaments are divided into segments. In this example, the MCL (blue) and LCL (yellow) are divided into 5 sections: 3 yellow ones separated by planes perpendicular to the central-local axis and a green one and a red one that respectively correspond to the femur attachment region and tibia.

The planes are defined using one of the two points on the central-local axis above mentioned and a vector that identifies the local orientation of the central line (Fig. 6).

The vector is found by taking two points on the central-local axis in the following way:

$$D = (x_1, y_1, z_1)\ \&\ Q = (x_2, y_2, z_2)$$

$$\overrightarrow{DQ} = (x_2 - x_1, y_2 - y_1, z_2 - z_1)$$

And subsequently, the plane is found with the following formula:

Vector $\vec{N} = (A, B, C)$ & point (x_0, y_0, z_0)

$$A(x - x_0) + B(y - y_0) + C(z - z_0) = 0$$

The partition of the ligament allows the reduction of the volume associable with the properties acquired during the mechanical test and leads to the increment of available samples. The assumption is that being the rupture a local event, it’s worth considering reducing the collection of data to smaller regions. However, it must be taken into account that the rupture might not happen perpendicularly to the local central axis or precisely along a plane (like a cut) but rather the fibres break individually until total rupture. For such reason, the partitions are conceptualized so that they are big enough to include the rupture region and at the same time allow the distinction of different regions of the ligament. It should be noted that in the sample used in this study the vast majority of ligaments ruptured at the attachment region with either the femoral bone or the tibial bone.

2.5 Statistical Analysis

Descriptive statistics were used to summarize the data collected and the results. Continuous variables were presented as mean values with their standard deviation/range. Linear mixed models for repeated measures were used to examine the association of MRI parameters and measurements with mechanical properties (stiffness, rupture force, elastic modulus and stress). MRI parameter (T1ρ) and measurements (cross-sectional area, volume), with and without ligament type incorporation, were included as fixed effects. Cadaver ID was included as a random effect. Conditional (fixed effects only) and marginal (fixed plus random effects) coefficients of determination (r^2) were calculated to provide information on the goodness of fit of the models/as a measure of model accuracy.

Differently from previous studies the dataset analysed in this research includes exclusively the $T_{1\rho}$ MR intensity parameter. Initially, it was planned to execute the experiments with all the MRI intensity available, however, the partial results discussed further in the section ‘Results’ showed no need to further evaluate T_2 and $T_2{}^*$as well.

The region specificity allowed by the image processing introduced at the early stages of this study affected the use of the mechanical parameters. Ligament stiffness and rupture force, derived from the tensile tests, are transformed into elastic modulus and stress.
Such parameters are calculated in the following way:

$$\delta(\text{elastic modulus}) = \frac{\sigma(\text{stress})}{\varepsilon(\text{strain})}$$

$$\sigma(\text{stress}) = \frac{F_{max}}{\text{cross sectional area}}$$

The use of the parameters described above better fit the region-specific approach that is adopted in the current study.

Intrinsically it’s assumed that the strain that corresponds to the elongation of the ligament happens uniformly along the ligament and, for simplicity, it’s assumed that the initial cross-sectional area is representative of the morphological evolution that characterizes the ligament when mechanically stressed.
The two used model have the following formulas:

$\delta = C_1 \times T_{1\rho} + C_2 \times \text{volume} + C_3 \times CSA$ with CSA = cross-sectional area

$\sigma = C_4 \times T_{1\rho} + C_5 \times \text{volume} + C_6 \times CSA$

Throughout the execution of the experiments the model is adapted to include the variable ‘ligament type’ as follows (Fig.12 is an example of ligament type inclusion):

$$\delta \ = \ C_1 \ \times T_{1\rho} + C_2 \times vol + C_3 \times CSA + C_{lig_{\delta}}$$
$$\sigma \ = \ C_4 \ \times T_{1\rho} + C_5 \times vol + C_6 \times CSA + C_{lig_{\sigma}}$$

2.6 The model

In this section is explained the reasoning that brought to choosing the mathematical model adopted for the analysis of the data.

The prediction model is made up considering the following elements:

- What are the types of data that should be analysed? As explained earlier in section 2.5 the parameters are chosen considering what can be extracted from the MR images that is considered to have a relevant impact on the mechanical properties of the ligaments.
- How can the data relate to each other? It must be taken into account, when choosing the model, the type of data that are to be correlated to each other. As reported in section 2.5 the mechanical data are transformed in order to be more representative of region-specific characteristics like the image-derived data are.
- Which fitting model algorithm fits best the dataset and the model with multiple variables and single output? The multiple linear regression has been chosen because it provides the required analysis of multiple independent to single dependent variable relationship. Moreover, this model simplicity has been favoured to other machine learning algorithms due to the small amount of data available together with the successful results reported by attempts in

previous studies [1]. Small dataset translates to fewer examples to be used to train the model. Hence, in scenario like the one reported here, a simpler model should theoretically be less demanding than a more complex mathematical layer.

Multiple linear regression is an extended or generalized version of the simple linear regression with multiple predictor variables (represented by the letter 'X') and a single scalar response variable 'Y'.

$$Y_i = \beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2} + \cdots + \beta_p X_{ip} + \epsilon_i$$

With observation number $i = 1, \ldots, n$ and p the independent variable.

2.7 Validation

The dataset has been split into 5 training subjects and 1 test subject, which corresponds to 20 training ligaments, 5 of each type and 4 test ligaments, 1 of each type. Each ligament is divided into 5 sections (or partitions) and the initial assumption was that the region-specific adaptation would improve the linear correlation.

The evaluation of the models that are created during the experiments is performed via qualitative analysis of the expected-versus-predicted graphs and the quantitative evaluation of the coefficient of determination (r^2) on both the training set and test set. The first is used to have a first impression whether the experiments that are being tested produce meaningful results. The latest parameter is defined as $r^2 = 1 - \frac{SS_{res}}{SS_{tot}}$ where SS_{res} is the residual sum of squares and SS_{tot} is the total sum of square (proportional to the variance of the data). In other words, it represents the proportion of the variance of the dependent variable that can be predicted from the independent variables. It normally ranges between 0 and 1, the higher the value the higher the correlation between dependent and independent variable, however, it can also yield negative values and that translates to very poor fitting of the model (or the intercept is not included, which is not the case in this study).

3 Results

The results presented here are a collection of multiple experiments obtained variating input and output parameters of the correlation model. This is done because very little had been obtained so far and consequently there are only hypothesis, that have yet to be tested, of what could be a satisfactory trainable model. As described in the section 'Validation' each model created for every experiment is evaluated on a training set and a test set.

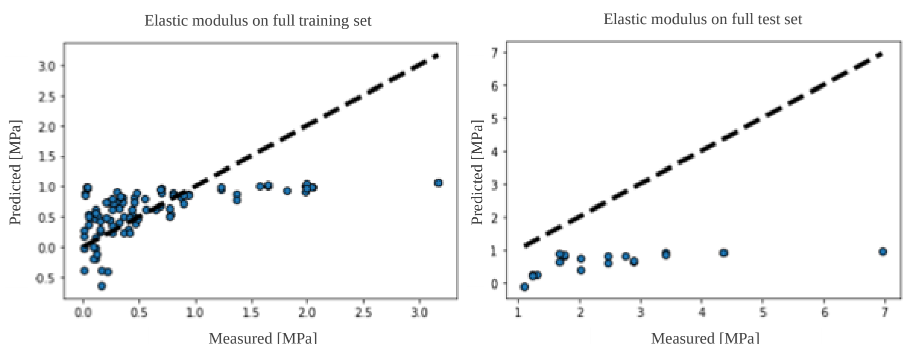

Fig.7 Actual versus predicted elastic moduli performed on the entire training set (left) and test set (right) [M*Pa*]. This experiment has been performed without distinguishing between ligament type nor partition. There are in total 100 training samples and 20 test samples.

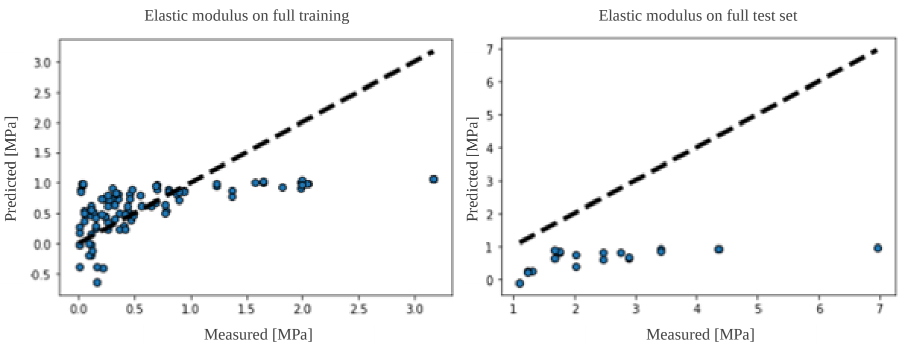

Fig.8 Actual versus predicted stress performed on the full training set(left) and test set (right) [M*Pa*]. This experiment, similarly to the one above, has been performed without distinguishing between ligament type nor partition. There are in total 100 training samples and 20 test samples.

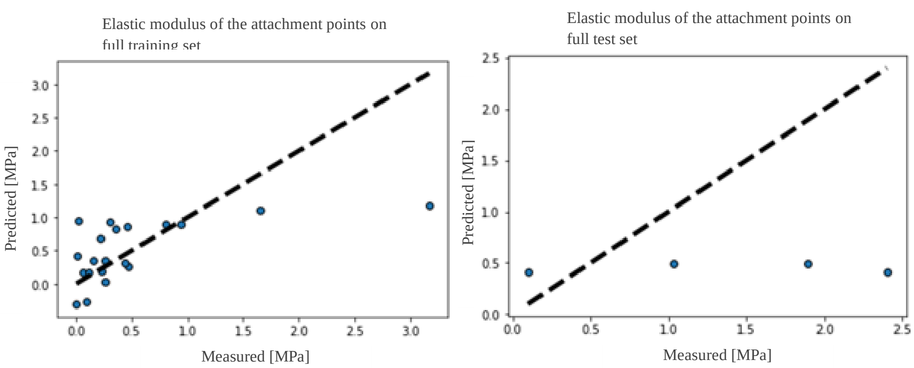

Fig.9 Actual versus predicted Elastic moduli exclusively at the attachment point of all the ligaments with the femur performed on the full training set(left) and test set (right) [M*Pa*]. This experiment has been performed using only the femoral proximity partition of each ligament. There are in total 20 training samples and 5 test samples. The same test has been conducted on all the other partitions following the same protocol.

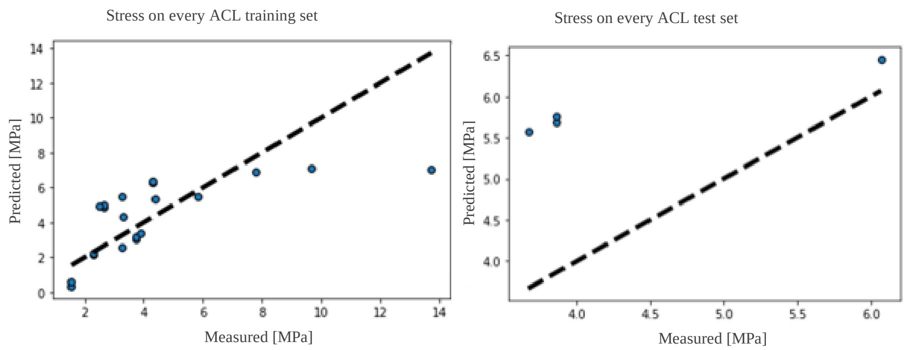

Fig.10 Actual versus predicted stress performed only on the ACL performed on the full training set(left) and test set (right) [M*Pa*]. This experiment has been performed on all the partitions of all the ACL type ligament available. There are 25 training samples and 5 test samples. The same test has been conducted on other all the other ligament types following the same protocol.

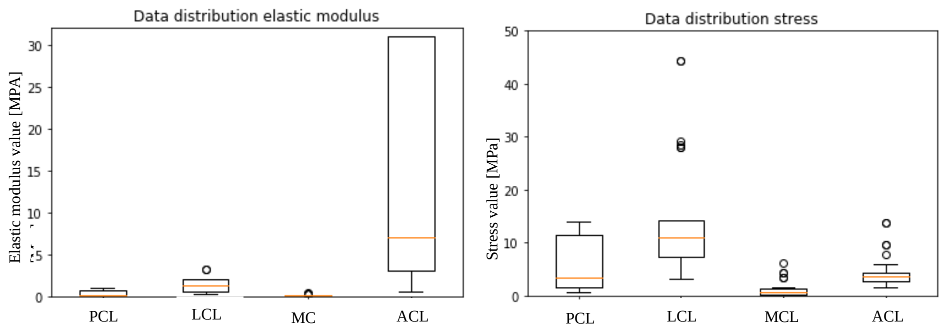

Fig.11 Analysis of data distribution differentiating the ligaments type for elastic moduli (right) and stress (left). This graph is included to show graphically how the data distribution varies greatly between ligament type and also between subject.

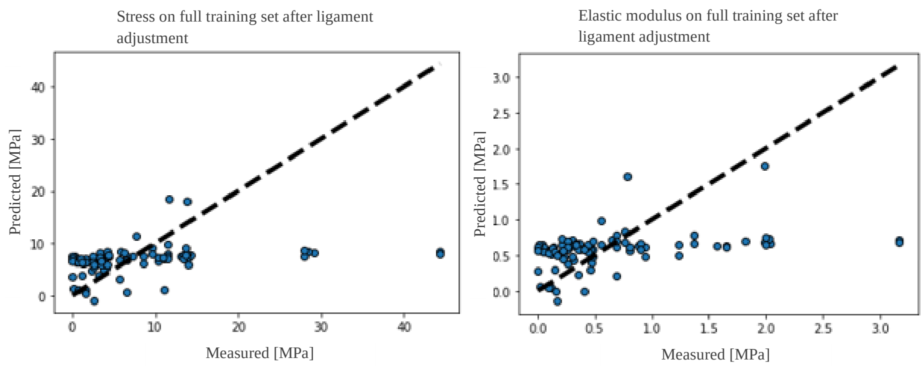

Fig.12 Actual versus predicted stress (left) and elastic moduli (right) performed on the full dataset after normalization of the dataset per ligament type [MPa]. This experiment has been performed distinguishing between ligament type with an extra parameter in the model formula but not on partition. There are in total 100 training samples and 20 test samples.

	Experiment using **elastic modulus** on ligaments **differentiating per partition**		Experiment using **stress** on ligaments **differentiating per partition**	
	r^2 training set	r^2 test set	r^2 training set	r^2 test set
acl	0.27	-3.55	0.48	-1.74
mcl	0.43	-3.37	0.42	-202.69
pcl	0.71	-71.5	0.65	0.84
lcl	0.75	0.58	0.48	-3.94
ALL	0.26	-1.05	0.3	-1.74

Tab. 1 Coefficient of determination of prediction evaluating the numerical values of the elastic module and stress on each type of ligament and all the ligament together while differentiating per partition.

Experiment using **elastic modulus** on **all** ligaments **only the femur region of contact**					
r^2 training set	0.36		r^2 test set	-1.71
Experiment using **stress** on **all** ligaments **only the femur region of contact**				
r^2 training set	0.17		r^2 test set	-33.52

Tab. 2 Coefficient of determination of prediction evaluating the numerical values of the stress evaluated on all the ligament type differentiating for partition of the ligament

4 Discussion

In this chapter the results are analysed to derive what can be observed and deduced from them. In addition, in the section 4.1, the method adopted in the execution of this study is compared with the methods adopted in previous studies for a complete overview of the state of feasibility of the objectives of the research.

In this study, the elastic modulus and stress of the tibiofemoral ligaments were correlated to quantitative MRI parameters and dimensional specifications. The results revealed that the region-specific model doesn’t show any improvement in correlation between the mechanical properties (elastic modulus and stress) and the image-derived parameters (volume, cross-sectional area and MRI signal intensity). The model showed little correlation on the training set and no capability at all of predicting with statistically relevant accuracy the mechanical properties.

The division of the ligament into smaller partitions, hence smaller sub-volumes, is possibly one of the reasons behind the poor correlation results. This is in agreement with the previous studies from Fleming et al. and Naghibi et al. [1] that

reported significant correlation strength between the entire ligament volume and stiffness and the rupture force.
Also, in this study, the mechanical parameters have been changed with the intention of them being more representative of region-specific events and converted from stiffness into elastic modulus and from rupture force into stress. These changes all together significantly influence the way the volume is included in the model possibly causing a major decrement in correlatability.

Further research into the statistical analysis revealed that the inclusion of ligament type enhances the correlation with the mechanical properties.
The result can be explained by the different type of collagen that ligaments are composed of. Ligaments share different percentages of collagen type I and type III. Wan et al. (2015) in a study investigating collagen type ratios in the ACL, PCL, MCL, and LCL, found that ligaments with more collagen type I are stiffer than those with more collagen type III [11].

Following the reasoning of the above-mentioned study and using the proportion between collagen type I and type III as a metric to measure the ligament stiffness results in a correspondence in the order of knee ligaments stiffness as derived from the statistical analysis in this study based on the ligament-specific coefficients. In accordance with Wan et al. (2015), the values acquired of LCL and ACL registered in average higher values compared to the other specimen types and also the order of magnitude of the elastic modulus and stress is in a comparable range. The model trained on the individual type of ligament appears to perform better than a single model that adjusts the prediction with a ligament type parameter. This is not surprising but the gap in performance could definitely be improved with a bigger sample size given that the ligament type dependency reduces the actual sample size from 24 specimens to 6.

Observing the plots and the tables it is noticeable that the general trend is that the model underestimates the actual response. Moreover, the numerical values not only confirm the previous statement, but it shows the failure of all the prediction attempts. Most of the experiments performed on the test set yields a negative value. Considering that the intercept is included in the built model these results translate to very poor prediction capability from the model.

The results show once more what had already been shown by the tensile tests, or else considerable inter-subject variability in mechanical properties of the ligaments (both stiffness and rupture force) as well as the variability of values between ligament of the same type (Fig. 11). This, once again and in addition to previous studies ([1], [14], [15]), reveals the essence of modelling the knee ligaments at a personalized level.

During the execution of this study, there have been several limitations. The limited number of specimens available surely limits the reliability of the models. The effects have been increased by the fact that each ligament type has different mechanical properties (as mentioned before, due to the different collagen type that composes them) and for this reason, it’s equivalent to a reduction of the number of ligaments. Considering the data distribution that can be observed in Fig.11 which shows high variability between ligament type and between the subjects, it is possible to conclude that a bigger sample size is needed.
It should be noted also that the specimens are extracted from relatively old donors. This translates to elastic modulus and strain values being skewed by the variable

age. In fact, comparing the values of initial rupture force and stiffness with the study conducted by Butler et al. who tested tissues from younger donors it possible to observe how the values of stiffness and rupture force used in this study are considerably lower on average. To the best of the Authors' knowledge, this is the first study assessing the correlation of mechanical properties of all four tibiofemoral ligaments to regional MRI parameters and dimensional properties, the 24 specimens and the current research still can provide valuable data for statistical analysis. Previous studies have already demonstrated how the ACL rupture force of an older donor of the same age range as the ones used in this study (61-97 years old) can be as low as 30% of the rupture force of the ACL in younger donors (22-35 years old) [21]. As a final consideration, it would be beneficial to include the age of the patient as a parameter to be taken into account whenever younger specimens are available.

4.1 Comparison with previous results

In this section the results obtained by the study conducted by Naghibi et al. [1] are compared with the results of this study as a conclusive analysis of the method adopted to carry out this research.

The comparison between the two studies can't be straightforward due the differences in the approach and it should be noted that the objective of the previous study was mainly on the extraction of the data (mechanical data as well as images). For this reason, the current method is adapted to create a model capable of producing an output as similar as possible to the previous one. The inputs for the model above are as follows: volume, cross-sectional area and MR intensity signal. It predicts stiffness and rupture force. The objective of this test is to verify how the two methods of data extraction (averaging value from the whole ligament, or analysing region specific characteristic) compare to each other. In order to match what has been done in the previous study the volume is obtained as the sum of the partitions' volumes and the cross sectional area as the average between all the partitions', possibly creating small differences in the final outcome. The MR intensity signal parameter is treated differently in the two studies because in Naghibi et al.'s [1] the signal is compared with a threshold to cut off the intensity value exceeding which it's considered noise. Such thresholding method has been attempted in this study as well, but it has been excluded because it could cause scenarios in which certain partitions are mostly empty.

The obtained results are shown below.

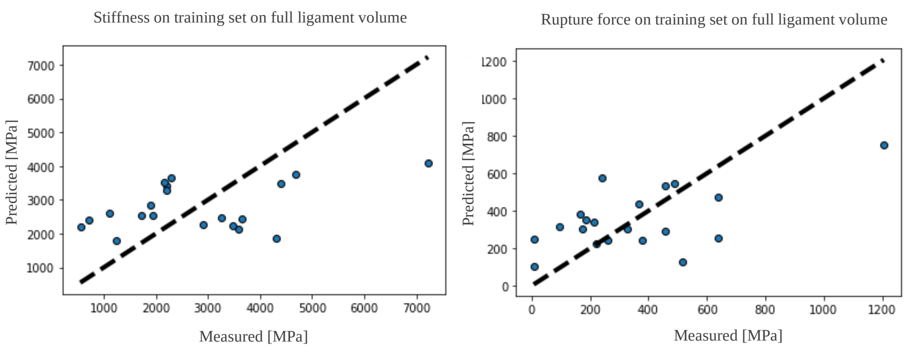

Fig. 13 Actual versus predicted values of stiffness(left) and rupture force (right) performed on a training set.

Comparing the plots reported here with the ones reported in the study of Naghibi et al. [1] it's possible to observe similar results between the two studies. It's reasonable to assume that the small differences can be attributed to the slight variation in the method adopted to extract the parameters. Overall, the results are comparable to the ones presented in the study mentioned above. At this stage, the interpretation of the results obtained in the current study compared to the previous one's highlighted the absence of experiment conducted on a test-set in Naghibi el al. [1] study.

This fact demonstrates that the region specific analysis is not strictly imputable as the cause behind the poor correlation obtained between image data and mechanical properties. In fact, if the previous study method, based on averaging the values of the entire ligament, didn’t satisfactorily prove the correlatability of the variables and the current study, based on region specific characteristics, didn’t accomplish so as well it’s plausible to find the cause of these results either on the incorrect assumption that the image data and the mechanical data can be properly correlated or that the dataset used in both studies is too little to accurately represent the variability of the data in relation to the adopted statistical model. Further investigation brought to create a test set and run it with the same method and correlational model that produced the graphs in Fig.13.

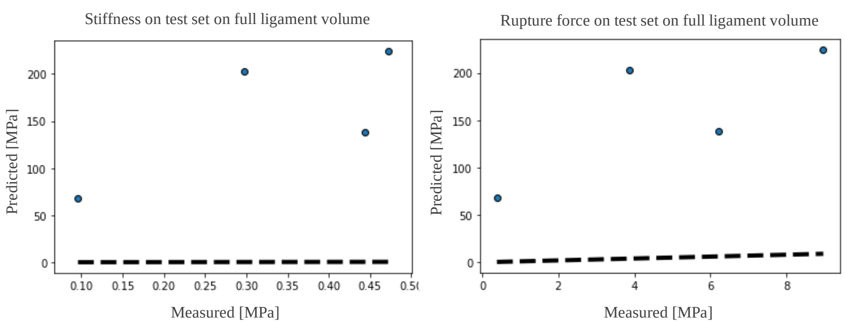

Fig. 14 Actual versus predicted values of stiffness(left) and rupture force (right). Results of the correlational model that recreates the method adopted by Naghibi et. al. [1] performed on a test set.

It can be noticed that the model is not capable of predicting the desired output. Concluding, it has not been possible yet to find a model capable of predicting the mechanical properties from MR images.

5 Conclusions

In this section are collected the conclusive ideas regarding the results obtained in the carrying out of this research.

Despite the attempt of obviating the lack of data by increasing the interest of the research towards regional characteristic the results are clearly showing that the model created is not capable of predicting the desired characteristics.
However, it's not straight forward to assert whether it is possible or not to find correlation in general between MR images and the mechanical properties of the ligaments.

The Author's feeling is that the training models created in this study showed decent results given the small amount of data and they also showed improvements when adjusted to fit to more specific scenarios (ligament type inclusion). This last point is interpreted as a sign of the existence of correlation.
Further research is needed to prove this last point, and it's strongly suggested that in doing so the amount of data is greatly increased considering also to include younger specimens to come closer to real life scenarios.

For what concerns the adoption of regional characteristics it's not easy to assess whether it is a better or worse method compared to the analysis of the ligament as a whole. There aren't sufficient elements to draw a conclusion. It's suggested to attempt to conduce experiments that account for regional characteristics given the knowledge of the exact region of rupture of the ligaments that are being analysed.

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