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Preface

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Chapter 1

Introduction

Patellofemoral pain syndrome (PFPS) is a painful musculoskeletal condition that is presented as pain behind or around patella [1, 2]. PFPS affects 6-7 % of adolescents, of whom two thirds are highly physically active [?]. Additionally the prevalence is more than twice as high for females than males.[3?]. PFPS may be present over longer periods of time where a high number of individuals experience a recurrent or chronic pain [?] and may also lead to osteoarthritis [3, 4].

Patellofemoral pain (PFP) is often described as diffuse knee pain, that can be hard to explain and localize [?]. Despite the fact that patients feel pain in the knee, there is not any structural changes in the knee such as significant chondral damage or increased Q-angle. There is no definitive clinical test to diagnose PFPS and it is thereby often diagnosed on exclusion criteria [3] to which PFPS is also described as an orthopaedic enigma, and is one of the most challenging pathologies to manage [?]. To assist diagnosis of PFPS, pain maps may be used as a helpful tool for the individuals to communicate their pain by drawing pain areas [5]. A study shows that through the use of pain maps it is possible to find a correlation between the symptom duration and the size and morphology of pain area [6]. Another method to measure pain is by using visual analog scale (VAS), that scores pain between no-pain to the worst pain imaginable [7]. However it is a known problem that chronic pain is considered as a multidimensional pain, because the perceived pain of an individual is influenced by biomedical, psychosocial and behavioral factors [?]

Since PFP is associated with a lack of knowledge, and it has been shown that there is a correlation between pain maps and duration and pain intensity, it is interesting to investigate if pain maps can be used to classify and predict PFP related information.

A method that has not been found used in this context before is a deep learning. The deep learning method is chosen for this study because it is a state of the art method, that has shown greater performance in specific computation fields, compared to other machine learning methods [8]. Furthermore the method is chosen because of its ability to find a non-linear connection between input and output data [8], which is found relevant for this study mainly based on the fact that PFP is subjective and may be affected by the multidimensionality of chronic pain.

The goals of this project is to explore how accurate a deep learning model can classify symptom duration and pain intensity associated to PFP pain maps using a limited dataset. Because the prevalence is more than twice as high for females than males, the gender is included as an input parameter for the model. Furthermore morphology of the pain maps is considered to be relevant, based on the indication that morphology and size of pain area increase with prolonged symptom duration. To investigate the influence of morphology three types of pain map representations are created: a binary representation, a simplified representation based

on knee regions and a combined representation that contains binary representations divided into knee regions.

1.1 Primary aim

The aim of this study is to explore classification performance of a deep learning model, using PFP pain maps and gender as predictors to symptom duration and pain intensity.

It is hypothesized that classification performance of the deep learning model is higher when using pain maps and gender to predict symptom duration than pain intensity.

1.2 Secondary aim

The further aim of this project is to investigate if multiple pain map representations affect the deep learning model classification performance.

It is hypothesized that different data representations of pain maps affect the performance accuracy of a deep learning model as related to the classification of symptom duration and pain intensity.

Chapter 2

Background

This chapter encompasses background knowledge that optimizes the understanding of essential topics in this project, such as patellofemoral pain and deep learning. Regarding patellofemoral pain it is relevant to get knowledge about the anatomy of the knee as well as pain and pain measurements if a deeper understanding of the syndrome is considered necessary. Furthermore, the chapter is essential for getting a basic understanding of some properties in the neural network models used in this project.

2.1 Anatomy of the Knee

The knee is the largest synovial joint in the body and consists of a hinge and a gliding joint. The hinge joint is placed between the lateral and medial femoral condyles and the lateral and medial tibial condyles. The gliding joint is formed between the patella and femur. The structure of the knee is illustrated in figure 2.1.[9]

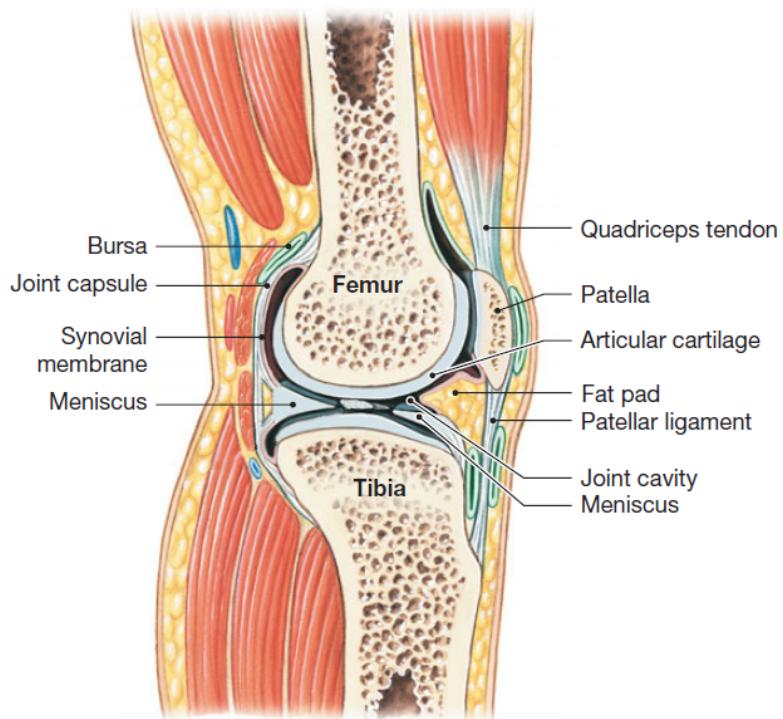


Figure 2.1: The figure illustrates the anatomy of the knee. Edited from [9].

It is shown in figure 2.1 that the patella is a sesamoid bone. At birth the patella consists of cartilaginous and ossifies when the child's extremities gets stronger, which typically proceeds between age two or three and the beginning of puberty.

The patella is surrounded by the tendon of the quadriceps femoris. Quadriceps femoris is the muscles which controls the extending of the knee. The quadriceps tendon is combined to the surface anterior and superior of patella. Tibia is combined to the anterior and inferior surface of the patella by the patellar ligament. The bones, tibia and femur, are covered by articular cartilage with the purpose of protecting the bones from friction. The articular cartilage on the two bones are separated from one another by synovial membranes that contains synovial fluid, that further reduce the friction. The primary functions of the synovial fluid is to lubricate, distribution of nutrient and absorption of shock.[9]

The fat pads and menisci are placed between the articular cartilages. The fat pads' function is to protect the cartilage and fill out space as result of the joint cavity changes. The menisci stabilize the knee and acts like pads, that conform shape when femur moves. In addition to fat pads and menisci the bursa acts as friction minimization between patella and tissues.[9]

There are three separate articulations in the knee joint. The first is between the patella and the patellar surface of the femur and the rest are between the femoral and tibial condyles. Additionally, the knee consist of seven major ligaments that stabilize the knee joint, which is shown in figure 2.2.[9]

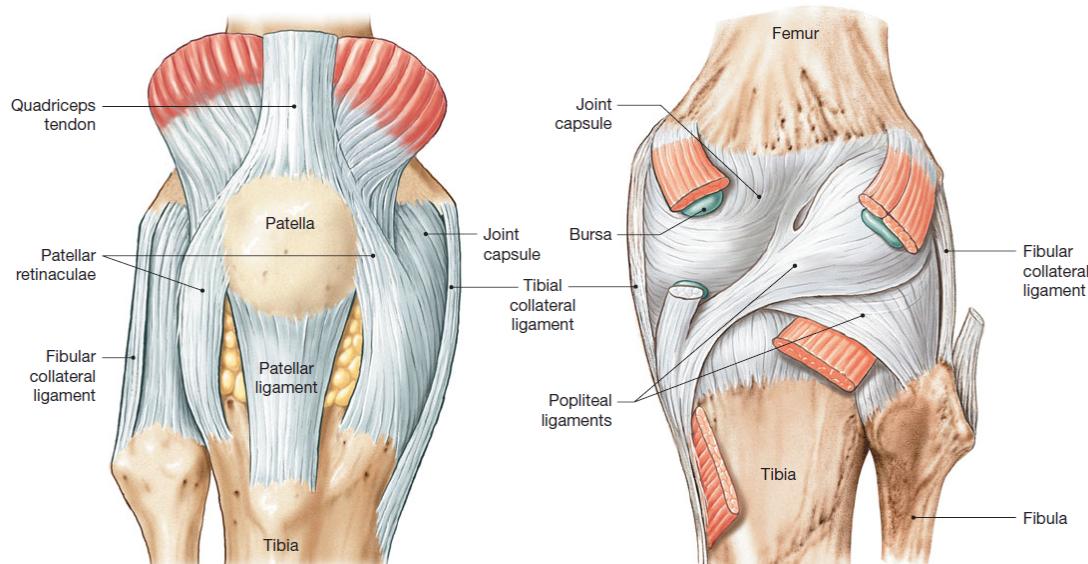


Figure 2.2: The figure illustrates the anatomy of the knee with focus on the ligaments. Edited from [9].

The ligaments patellar retinaculae and patellar ligament support the anterior surface of the knee. When the knee is fully extended, the tibial and fibular collateral ligament are responsible for stabilizing the joint. Between femur and the two lower bones in the leg, tibia and fibula, is the location of the two popliteal ligaments, which stabilize the posterior surface of the joint. In addition to the visible ligaments in figure 2.2 there are the anterior cruciate ligament (ACI) and posterior cruciate ligament (PCL) in the joint capsule. The two ligaments cross each other and are connected to the tibial and femoral condyles. They reduce the movement, anterior and posterior.[9]

As previously mentioned the gliding joint is formed between the patella and femur, so that during knee movement patella is gliding up and down at the femoral condyle. A condition associated with incorrect movement of the patella, is patellofemoral pain syndrome (PFPS),

that occurs when the patella moves outside of its ordinary track, which for instance can be movement in lateral direction.[9]

2.2 Pain

The International Association for the Study of Pain (IASP) has defined pain as being “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” [10, 11].

Humans are aware of the surroundings and threats to their bodies because of the pain. The pain indicates that there might be a risk for permanent damage on the body, which refrain humans from danger and therefore increases the chances of survival.

Pain can be either nociceptive or neuropathic. Nociceptive pain is associated with tissue damage. This type of pain is related to the nociceptors, which are receptors with a high threshold that when stimulated may give the perception of pain in tissues [12]. Neuropathic pain occurs central from the nervous system. This pain can be caused by illness or physical damage.

Furthermore, pain can be divided into three categories: acute pain (less than three months), persistent or chronic pain and cancer pain.[13] Additionally, the sense of pain can be divided into some qualities, which is shown in figure 2.3.

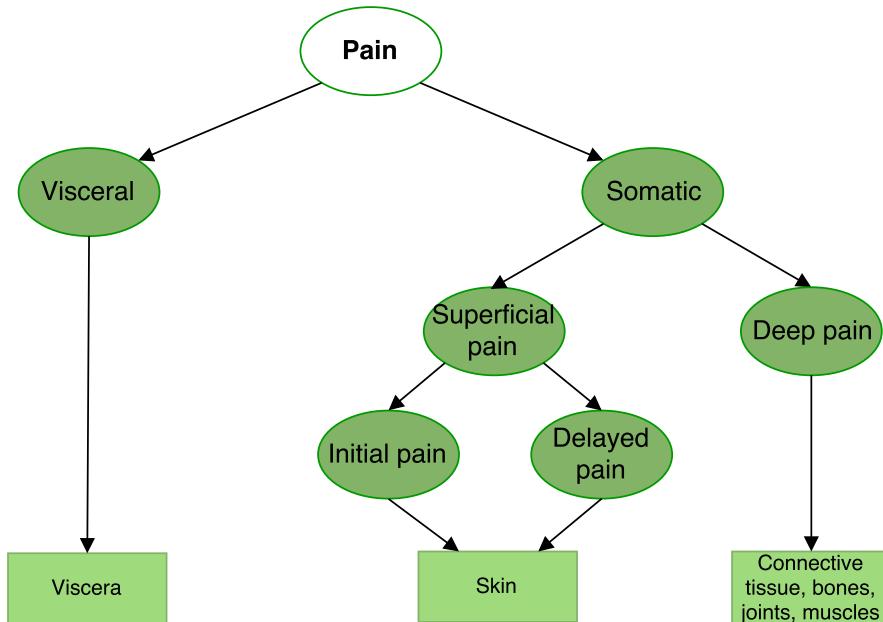


Figure 2.3: Model of pain qualities. Ovals with green background represent qualities of pain. The rectangles show where the pain occurred. Edited from [12].

Pain can be divided into two qualities; visceral and somatic pain. Examples of visceral pain include pain associated with gallstone and appendicitis. This pain can be characterised as a dull or diffuse feeling. Somatic pain is subdivided into superficial pain and deep pain. If the pain derives from the skin it is superficial pain, which furthermore is divided into initial pain and delayed pain. The initial pain is the first pain that is received, and this pain is characterised as sharp and localizable. The delayed pain, also known as the second pain, is sensed as a dull or burning pain that occurs after a half to one second. This pain is more

difficult to localise than the initial pain and lasts longer.[11, 12] The other somatic pain is deep pain, which is associated with pain from the muscles, bones, joints and connective tissue. This pain is described as a dull pain and it radiates into the surrounding tissue, which makes the exact pain area hard to point out.[11, 12]

Since the aetiology of PFPS still remains unclear [2], it is hard to place this type of pain in addition to nociceptive and neuropathic pain. But PFPS can be classified as deep pain and acute or chronic pain. Since the PFPS is often longer than six month it is described as a chronic deep pain.

2.3 Identify and interpret pain

There are many ways to identify and interpret pain. To identify pain and find some physical damage that causes the pain can objective methods be used. Subjective methods is used to interpret pain for collecting knowledge of the subjects pain intensity, behavior and how it is experienced.[14]

2.3.1 Identify cause of pain

A objective pain measurement is often used when a subject experiences knee pain where a clinical examination of the knee can occur. This examination involves i.a. provocative tests, such as anterior and posterior drawer test, Lachman's test and pivot test that examines the integrity of the ACL and PCL. Furthermore is McMurray test which test for meniscal tear.[15] Illustrations of the tests are shown in figure 2.4.

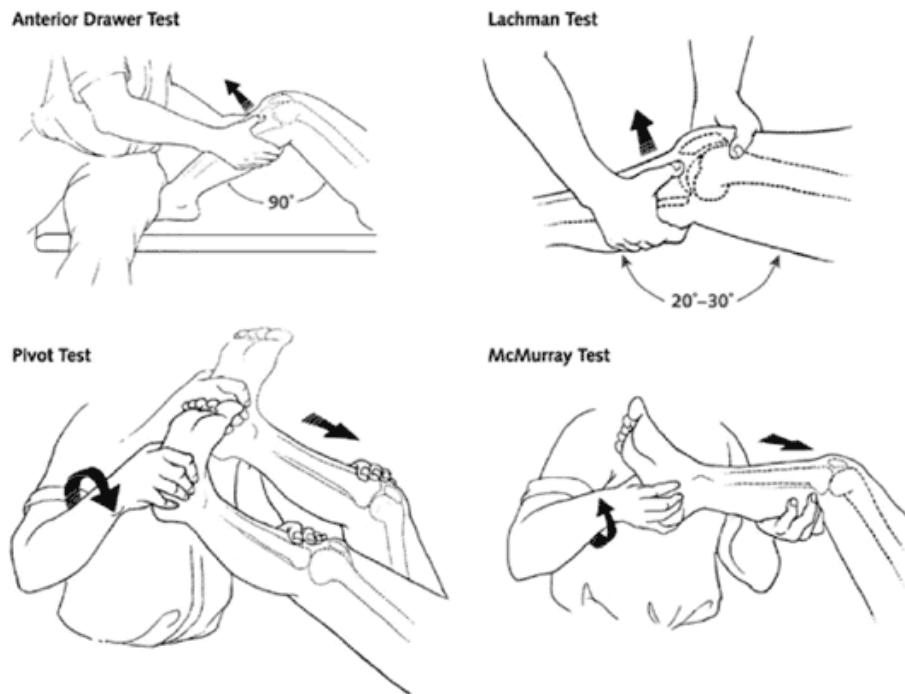


Figure 2.4: Clinical examination with provocative tests; Anterior Drawer Test, Lachman Test, Pivot Test and McMurray Test.[15]

In addition to clinical tests there is some paraclinical tests such as X-ray and MRI, but PFPS does not show any structural changes in the knee, like increased Q-angle or significant chondral damage [3], which makes it difficult for healthcare personnel to treat the subjects.

2.3.2 Pain interpretation

Pain is experienced and perceived subjectively [10, 14] and is dependent on personality and character [12], which is why it is important to measure the pain from the subject's perspective. One of the most commonly method used to measure pain intensity is Visual Analogue Scale (VAS) [16]. VAS is often used in clinical and research settings, where the subjects mark their pain on a scale from no-pain to the worst pain they can imagine.[7] A illustration of a VAS is shown in figure 2.5.

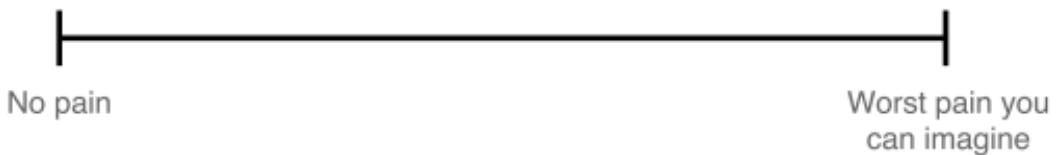


Figure 2.5: Visual Analogue Scale (VAS). Edited from [7].

Additionally to mark pain on a scala is questionnaires used to define subjects pain. An example on a questionnaire is Knee injury and Osteoarthritis Outcome Score (KOOS), which contains questions about symptoms, stiffness, pain, function daily living, function, sports and recreational activities and quality of life. When the subjects fill the scheme a score between zero and one hundred is achieved. A score at zero represents extreme knee problems, whereas a score at one hundred represents no knee problems.[17] The questionnaire can be seen in Appendix A.1.

Since PFPS is describe as a diffuse pain, where subjects indicate their pain by 'placing both hands over their knees', is it hard for subject precise communicate their pain. Thereby is pain mapping a method for subjects to better indicate and communicate their pain.

Pain mapping

Pain mapping is a technique, that Harold Palmer introduced in 1949 [18], which is used to transfer a patient's perceived pain into an objective graph or map by drawing the pain area. Pain drawings can be made by the patients who draw their pain areas on a body outline. Pain drawing can also be made by observers who observe the patients and then draw from the signs the patients are showing. An example of a body outline is shown in figure 2.6. Sometimes a questionnaire is added to the pain drawings to get a more detailed overview of the pain to determine parameters associated with the pain. These parameters can also be useful in determining the source of the pain.[19]

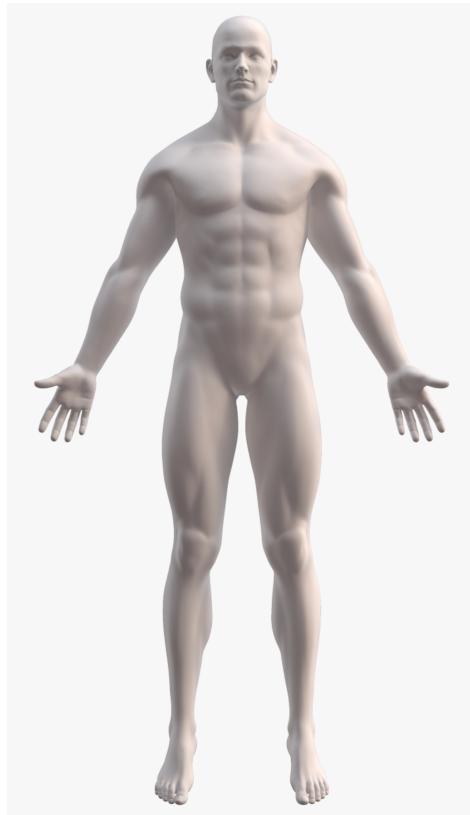


Figure 2.6: The figure illustrates an anterior body outline for pain drawing. The figure is a screenshot from the application Navigate Pain.

Pain mapping are commonly used in clinical practice [19], and can be useful for patients when they try to describe their pain. Pain maps may also be helpful in diagnosing patients and follow-ups during or after treatment to get an indicator of the patient's response to the treatment.[5] According to Schott there are some issues with the graphical representations of pain, some of which are problems with drawing a three-dimensional feeling of pain on a two-dimensional surface, and distinguishing between internal and external perceived pain on a map.[19]

2.4 Knee regions

Patients with PFPS often describe the knee pain as a diffuse pain, and when looking at pain drawing samples from multiple patients it is also evident that there is a high variability in the distribution of pain patterns across different areas of the knee.

To distinguish between different pain areas, the knee can be divided into various regions as seen in figure 2.7, where atlases of the left and right anterior knees are illustrated. The divisions is inspired by Photographic Knee Pain Map (PKPM) which is designed to categories location of knee pain, diagnostic and research purposes. PKPM represent both knees that makes it possible to identify unilateral and bilateral pain.[?]

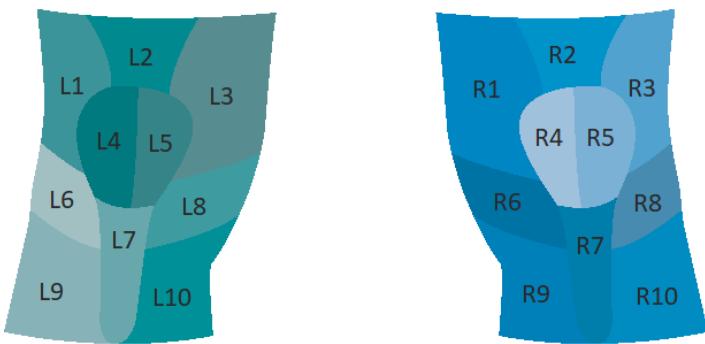


Figure 2.7: The figure illustrates atlases of the left and right knees, where each knee is split into ten regions.

The regions are based on the anatomic structures according to the areas where subjects often indicate pain. There are ten regions, where region 1 and 3 represent the superior lateral and superior medial areas for patella. Region 2 refers to quadriceps tendon. The patella is divided into lateral and medial regions, which are region 4 and 5. Region 6 and 8 are lateral and medial joint line areas. Patella tendon is region 7 and the two last regions, 9 and 10, are tibia lateral and medial.[?]

2.5 Machine learning

Machine learning describes the use of algorithms to make a system able to identify different data types, like images or text, for transcription of speech into text, matching news items, posts or selection of relevant results of search [8]. Machine learning is a method that uses inductive inference in order to identify rules in a dataset from given input and output [20]. If the computer learns this feature, it can be used to make intelligent decisions and predict specific outcomes.[20] It is a field that has seen a lot of progress over the past decades, partially because developers recognize the ease in training a system only using examples of the desired in- and output behavior. This is simply easier than trying to manually write a piece of code that anticipate different scenarios from different input types.[21]

2.5.1 Deep Learning

Deep learning is a branch of machine learning. The main difference between the use of machine learning and deep learning, is that machine learning is not suitable for handling raw data form. Instead a machine learning system often needs a feature extractor, that will generate a feature vector from the data that can be used as an input for the machine learning system. Deep learning is based on different techniques that makes it able to handle that data in its raw form, mainly because of its structure.[8, 22] Because of this the system will automatically detect the necessary representations needed for classification and detection. Neural network is a structure of deep learning which consists of different layers, that can be divided into a input-layer and an output-layer, with one or more hidden layers in between [22]. The key aspect of these layers is that the features are not defined by programmers, but they are found and learned from raw data using a general-purpose learning procedure.[8] An example of the structure can be seen in figure 2.8.

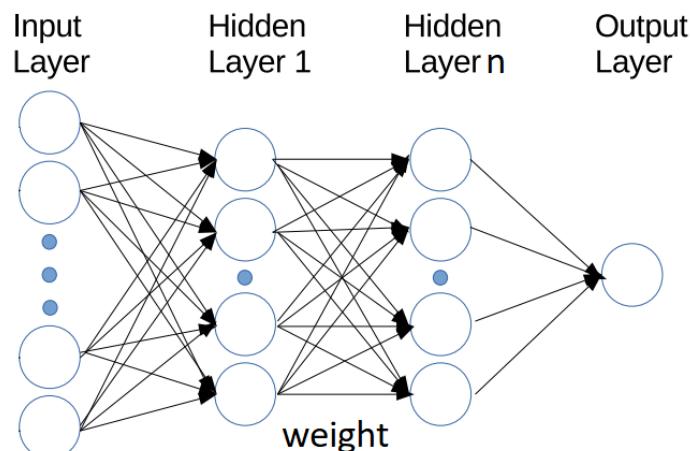


Figure 2.8: Example of the neural network with possible layers[23].

The different layers consist of a series of nodes, where each node is connected by weights to one or several other nodes from a different layer. In the input-layer the nodes are fed with the data that the system is given. The second layer will then receive the output from the previous layer, and this process continues through the layers until the output-layer is reached.[22] An example of how the hidden layers affect an image can be explained as follows: Firstly, the system detects minor changes like edges. Secondly, the edges are compared and put together

to make up different kind of shapes. In the third hidden layer, it will be further combined to make up an object that can be identified.[8]

Learning scenarios

There are three main learning scenarios: supervised, unsupervised and semi-supervised learnings.

Supervised learning is the most common way of training in machine learning [8]. When using this method the system is trained with labeled data, where the generated output can be compared with an expected output, and thereby see evaluate the performance of the system. The weights are interconnection between two layers and they work as a set of coefficients, defining an image feature.[24] By adjusting weights in the neural network it is possible to fit the model better to the training data, and thereby increase its accuracy and reduce error [8]. Supervised learning is mostly associated with classification, regression, and ranking problems [25]. Differently from supervised learning the input in unsupervised learning is received with unlabeled data and the predictions. Then the system organizes the data by searching for common characteristics [25]. An example of an unsupervised learning algorithm is clustering, where the unlabeled dataset goes through a classification, and split into different classes.[26] In semi-supervised learning the learner is receiving both labeled, unlabeled data and then it searches for common characteristics in data. It is used mainly when the labeled data is hardly collected and unlabeled data is easily reachable.[25]

Learning curves

During the beginning of training, the training error of network will typically be relatively high, but during training the error decreases monotonically, as the weights are adjusted in the network [27]. An illustration of how the error values are affected during training can be seen in Figure 2.9.

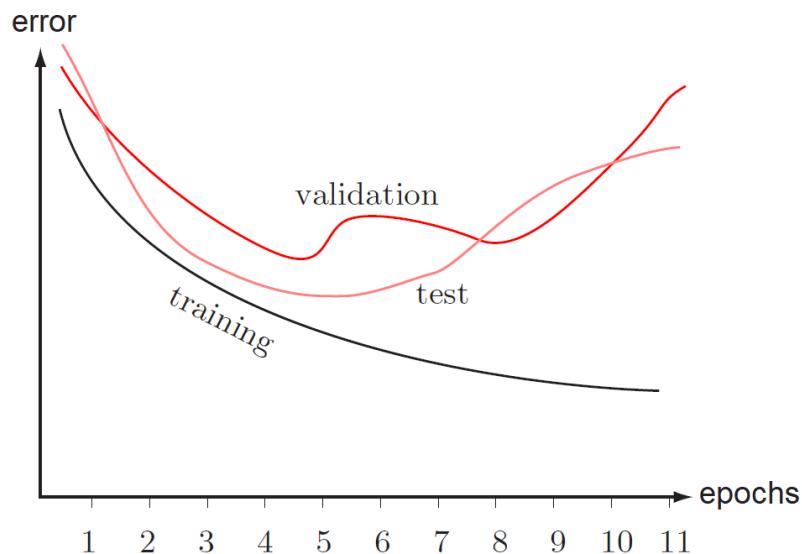


Figure 2.9: Illustration of how training (black), validation (red), and test (orange) error is affected by the increase in epochs. Edited from [27].

From the figure it can be seen how the error value of the validation, can be used to evaluate the network. Near the fifth epoch the validation and the test error starts to rise, indicating that the network is overfitting to the training data, thereby decreasing the generalization abilities. Validation error can therefor be used as stop criterion for when the training is optimal, and prevent overfitting. Typically the validation and test error will always be higher than the training error, which is also seen in Figure 2.9. [27]

Back-propagation

Backpropagation is a popular learning algorithm in neural networks, that is based on gradient decent, and valuable because of the simplicity and computationally efficient. [28, 27]

Backpropagation is the process where the weights are adjusted to reduce the error between the input and desired output of the model. This also makes backpropagation the most general method used for supervised learning where the error is calculated through the used of the network's output and a real output.[27]

The different operating-phases of the can be split into a feedforward and learning phase. Feedforward is when the input is fed into the network and and output is given, simply by passing input through the different layers and weights. When the network is trained that weights are initiated with random values, from which the result is a low performance accuracy of the network. The learning phase is then again related to supervised learning, where parameters like the weights are adjusted to reduce error during training. [27]

In the backward process, weights will be updated to minimize the error between input and output layers. This process will be applied until optimal weights with minimum error is reached.[24]

The basic idea behind it is to minimize the overall output error as much as possible during the learning stage. This algorithm process is divided in two main stages: forward and backward. In the first process (forward), the back-propagation architecture is described as the inputs and weights multiplication of each node (separate input) summed with additional coefficients called biases.[24]

- There are simple methods that can be used to improve performance and training speed. Scaling of the input and giving an initial weight [27]
- The architecture is important for classification, and depends on the given problem [27].
-

2.5.2 Convolutional Neural Networks

Convolutional neural networks (CNNs) perform highly in several tasks, including digit recognition, image classification and face recognition. The key aspect of CNNs is to automatically learn a complex model by extracting visual features from the pixel-level content. CNNs are feed-forward models that map input data with a set of suitable outputs. Accuracy and performance rely on large training datasets and training procedure based on back-propagation with optimization algorithm such as gradient descent which is used for finding minimum value of the function.[23]

Chapter 3

Methodology

3.1 Pre-processing

The data is pre-processed in MatLab to prepare it to the three different neural network models. Each model has an appurtenant data representation which are prepared in three different ways. The three data representations are morphology, regions and superimposed morphology and region. Common for the data representation is that the pain maps are imported as image-matrices whereafter the matrices are resized, since the given data was collected at different resolutions (screen sizes). Furthermore, the matrices are cropped to sort out unnecessary data like the areas inferior and superior to the knee. Before the data is used as an input in the neural network models, the image-matrices are converted into vectors whereafter they are assembled in one matrix for each data representation. To get additional information associated with the pain maps, is gender added by including a column vector to the three matrices. In addition to the input, the neural network models need an output to train the models. The output, which is either symptom duration or pain intensity, is likewise added as a column vector. The following sections describe the pre-processing of the individual data representations.

3.1.1 Morphology

The first representation of data is a binary matrix of the original pain maps. Firstly, the image of the original pain map is gray-scaled to get a one-dimensional matrix instead of a three-dimensional RGB-matrix. This matrix is then converted into a matrix consisting of zeroes and ones, where the pain pixels are symbolized with ones. An original pain map and a pain map consisting of a binary matrix is shown in figure 3.1.

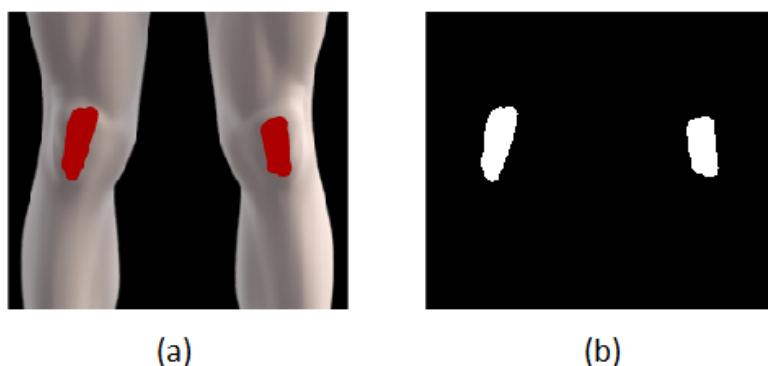


Figure 3.1: (a) Original pain map and (b) image consisting of a binary matrix where white color represents the pain pixels.

An illustration of this data representation is created to convey how the data is assembled and transferred to the model. The illustration is shown in figure 3.2.

	Binary image-matrix												Gender Duration/ pain intensity
Image-vector 1	0	0	0	0	1	0	0	1	0	1	2		
Image-vector 2	1	0	0	1	0	1	1	0	1	0	0		
Image-vector 3	1	0	1	0	0	1	1	0	1	0	1		
Image-vector 4	0	1	1	1	0	1	1	1	0	1	0		
Image-vector 5	1	0	1	0	1	1	1	0	0	0	2		
Image-vector 6	0	0	0	1	0	0	1	1	1	1	1		
Image-vector ...	1	0	1	0	0	0	0	1	1	1	1		
Image-vector n	0	0	1	1	1	1	0	1	1	1	0		

Figure 3.2: An illustration of the matrix of the morphology data representation. The matrix consist of image-vectors for each subjects where the two last column indicate the appurtenant gender and either duration or pain intensity. The image-vectors has a length equal to the number of pixel in the pain maps.

3.1.2 Regions

The second representation of the data is a matrix consisting of vectors with 20 values which indicate pain in relation to the knee regions. The knee regions shown in figure 2.7 are converted into a matrix consisting of 20 values, which represent each knee regions. This matrix is superimposed to the binary image of the pain map, which results in a matrix with pain represented in each knee region. In figure 3.3 are the knee regions and the pain associated with the regions illustrated.

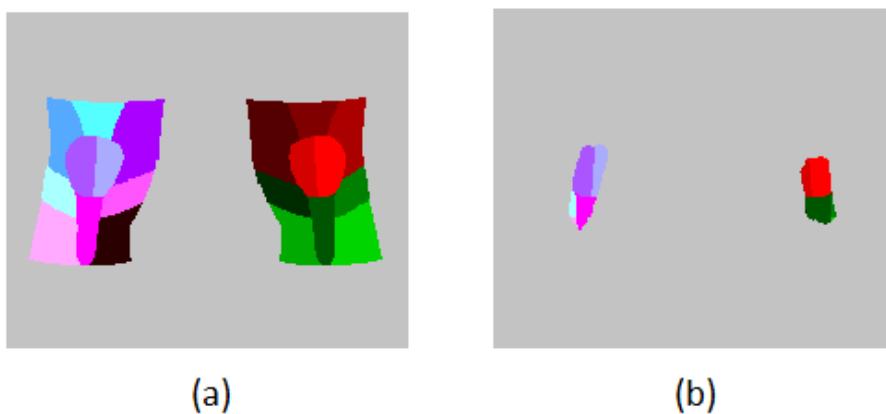


Figure 3.3: (a) Knee regions and (b) pain in the specific regions.

After superimposing the two matrices, knee regions and pain, the number of pixels in each active knee region is found. This number is compared to the total number of pixels that are in each knee region, so knee regions with less than 15 % pain are excluded. WHY 15%.

As a result a vector with 20 values is created. This data representation is implemented the same way as the first representation, figure 3.2. The only difference is that the length of the image-vectors respond to the 20 regions, and therefore are there only 20 values in this data representation.

3.1.3 Superimposed morphology and regions

The third representation of the data is a matrix consisting of individuals' pain divided into the knee regions. In this representation the superimposed matrix from the second data representation is used. Since the data representation should reflect the morphology of the pain and divide the pain into the different knee regions is one-hot encoding used. One-hot encoding is a way to separate categorical data into binary data [31]. This means that the 20 values for each knee region do not have a correlation. After one-hot encoding the superimposed matrix consists of 20 layers where each layer represents a knee region. An illustration of this data representation is shown in figure 3.4.

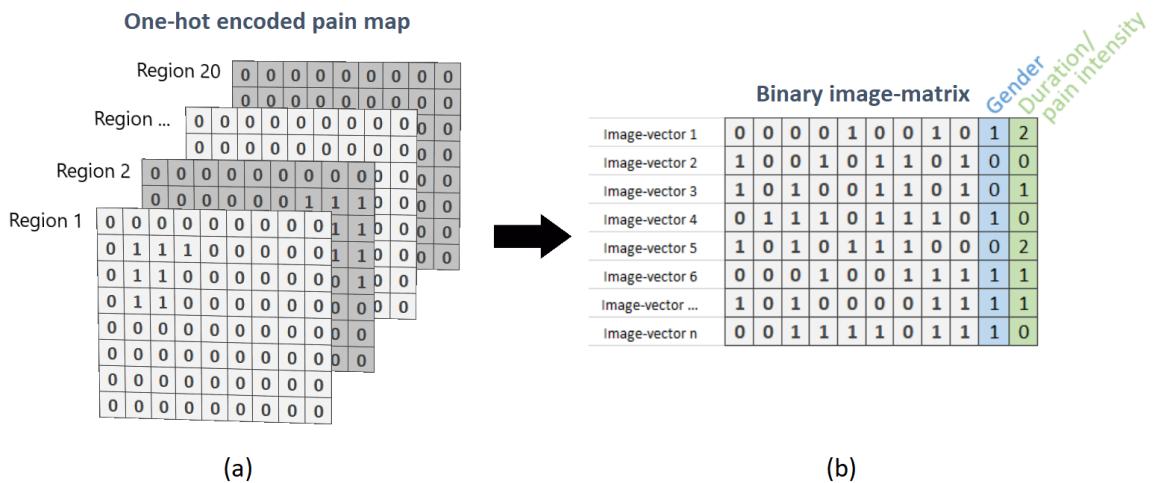


Figure 3.4: (a) illustrates the one-hot encoded pain map and (b) shows the images-vectors in one assembled matrix with gender and either symptom duration or pain intensity.

Chapter 4

Materials

This chapter creates an understanding of the given data and the different programs respectively the program where pain maps are created and the program for development of the neural networks.

4.1 Data

Data used in this project were collected beforehand from an on-going FOXH trial which is conducted in collaboration with Danish and Australian universities. The data consists of pain maps which were drawn by subjects with PFP through the use of an application Navigate Pain in a clinical setting. The data contained information regarding the subjects in terms of i.a. age, gender, height and weight. For each individual subject information related to the PFPS was also collected, regarding the duration of PFP, pain intensity and which knee was the most prominent for pain. The number of samples available during this study was collected from ??? subjects with PFP. An example of a pain drawing can be seen in figure 4.1.



Figure 4.1: Pain drawings of the lower extremities. The red markings indicate the area of pain perceived by the individual subject. In this case the PFP is bilateral (on both knees).

4.1.1 Software application: Navigate Pain

Navigate Pain is a software application that is used to visualise the location, shape and spatial distribution of pain from patient to healthcare personnel. The application permits individuals to draw their pain into a body outline with different colors and line thickness. Navigate Pain android was developed at Aalborg University and a commercial web application is available at Aglance Solutions (Denmark).[29] Figure 4.2 illustrate the process using the application.

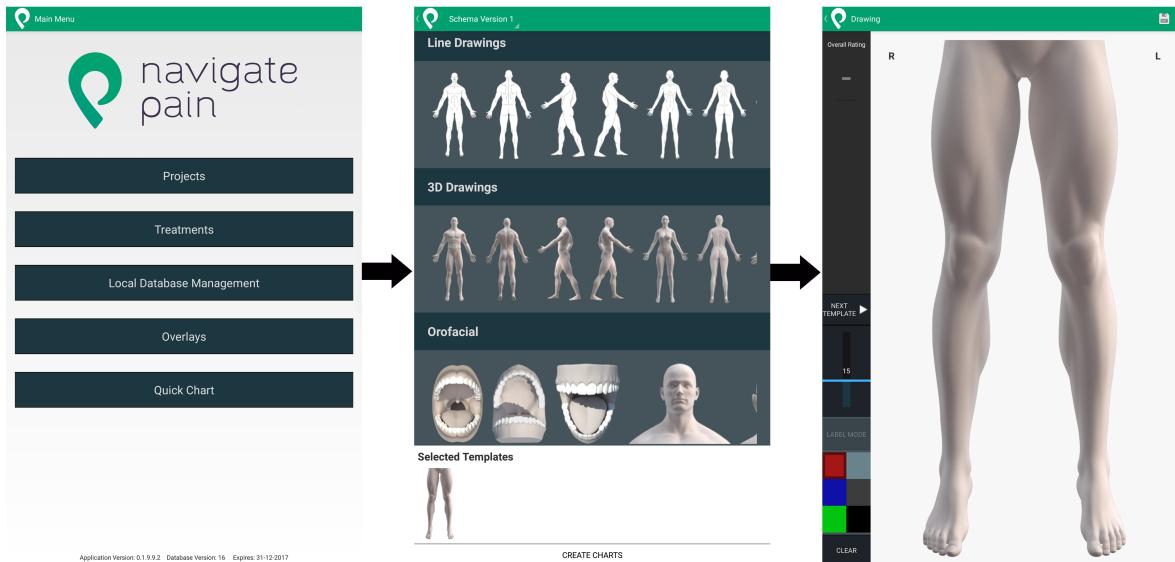


Figure 4.2: The figure illustrates the process for making a pain map with Navigate Pain. There is three screenshots of the application.

The left screen in figure 4.2 is the main screen. By clicking on "Project" a folder with subjects is created. From each subject information like name, age, height is saved. Before the subject can draw their pain areas, the body outline has to be chosen, which illustrates the screen in the middle. The body outlines is divided into five categories: Line Drawings, 3D Drawings, Orofacial, Special Zooms and Knee Pain. In the bottom the selected templates is shown. When clicking on "CREATE CHARTS" the right screen is shown. Here it is possible to draw the pain areas with different colors and line thickness, which can be seen in the left side of the screen. Afterwards the pain map can be saved.

4.2 Programs

In this project it is chosen to use Python v3.6.3 for development of the neural network. Python is an object-oriented and general-purpose programming and scripting language. Python is among other things used for programming websites, mobile applications, desktop GUI's, but also used for machine learning programming. When developing a machine learning application, there are different libraries that can be used, where some of the most popular is the Theano and the TensorFlow libraries.[30]

In this project the TensorFlow v1.3.0 library has been used. TensorFlow is an open source library for development of machine learning applications, that has been released by Google [30].

maybe something about keras... if we are gonna use it. Keras is a high-level neural network library, that runs on top of either TensorFlow or Theano. Keras is a simplified version of the two libraries, which makes it easier to program in Python, but still allows for building complex models.[30]

Chapter 5

Results

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Appendix A

Appendix

A.1 Appendix I