Contents

Statistical shape modelling of osteoarthritic knee joint

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Layman's summary

Osteoarthritis (OA) is a disease that occurs in the joint, and it is mostly caused by the deterioration of the cartilage and other soft tissues. The purpose of the cartilage is to absorb shock and provide a smooth surface to allow the bones to move fluidly. Damage to the cartilage can lead to bone attrition, subchondral sclerosis (thickening of the bones), asymmetric joint-space narrowing, osteophytes (bone spurs), and other issues.[1] These consequences of OA give the bone a unique shape and can cause pain, swelling, and inflammation to the joint. In its worst cases, can reduce functionality and for this reason, is considered the leading cause of disability for elderly individuals. Currently, there are no treatments to cure OA, but only to manage symptoms.[2,3] Moreover, no imaging biomarkers exist for this pathology, even if it has been demonstrated that changes in bone shape can be found even one year before other symptoms of OA are explicit in radiographs. This could help design treatments for subjects at risk of developing OA before the progression of more serious symptoms.[2] For this reason, it is important to find a way to model the knee joint considering bone shapes and joint. The anatomy of the single bones in the joint (tibia and femur) can be reconstructed by 3D imaging techniques like Magnetic Resonance Imaging (MRI) or Computed Tomography (CT), and images in the same dataset are aligned and compared using a common coordinate system. Other interesting information, however, can be found in images scanned in weight-bearing conditions, with the subject standing instead of lying in a supine position. The joint space narrowing of the tibiofemoral joint, for example, is an important parameter to assess the severity of OA, and it can be properly measured only if the patient is standing, which is not possible in 3D scanners, but only in radiographs, that produce 2D images.[2,4] To this end, the aim is to merge the two types of information: the exact representation of the anatomy of the bones in the joint (that can be gained from the 3D scan) and the position of the bones in the constraint of the joint (which can be desirably estimated from images taken under load of standing position). Among the many examples cited in this study, registration between these two types of images seems to be a suitable solution for this particular issue. From the two images, a series of landmarks are chosen and aligned, and the positioning of the 3D model changed according to the relative position between the bones in the 2D image. The result is a 3D model that represents accurately the knee joint, which thanks to Principal Component Analysis (PCA) can then be described in an extremely compact way.[5] Depending on the type of images available, other methods have been discussed to describe knee anatomy and positioning, with particular focus on imaging of knee osteoarthritis.

Abstract

Osteoarthritis (OA) is a degenerative joint disease caused by the deterioration of the cartilage within a joint. It is diagnosed in around 1 in 7 adults, and it is the leading cause of disability among elderly individuals. OA occurs frequently in the knee joint, causing pain, inflammation, swelling and, in its worse cases, reducing functionality. From imaging, it manifests as osteophytes, subchondral sclerosis, bone attrition, and asymmetric joint-space narrowing, leading to a unique shape of the bones.[1] Currently no early biomarkers exist for this pathology, and pharmacological treatments only target symptoms, but not its cause. It has been proven that changes in bone shape can be found even more than one year prior to the onset of radiographic OA, and the joint space narrowing seems a good candidate to be used as biomarker. In order to be properly visualize the joint space, however, imaging needs to be performed in a standing position. This is only possible in radiography (which provides 2D images) and not in 3D scan as Magnetic Resonance Imaging or Computed Tomography (which can provide an accurate 3D model of the joint). In this study, different ways to create statistical shape models that can provide accurate information on the anatomy of the knee joint under load are described, and currently registration involving 2D and 3D images seems to be the most suitable solution.

Introduction

Osteoarthritis (OA) is a degenerative joint disease caused mainly by the deterioration of the cartilage within a joint. It affects multiple joints and their internal structure, changing the anatomical and/or physiological shape of the tissues. The symptoms include pain, swelling, stiffness, and in its worse cases reduces functionality, affecting the quality of life. From a study from 2008 to 2014, one in 7 adults in the US was affected by OA, and it is the leading cause of disability among elderly individuals.[2,3] Risk factors include sex (more prevalent in female subjects), obesity, genetics, major joint injury, and age as around 30% of individuals over 45 years of age present radiographic evidence of knee OA, of which half of them present symptoms with different degrees of severity.[6]

At the moment, no therapy is available to prevent OA or its progression, and the current pharmacological treatments only target symptom, but not its cause. Therefore there is a need to find an imaging biomarker that could improve the development and testing of treatments and help finding subject at risk of developing the disease.[2,7] It was demonstrated, in fact, that changes in bone shape can be found even more than one year prior to the onset of radiographic OA, opening the possibility of treatment for persons at risk of developing more serious symptoms.[2]

In knee osteoarthritis, medical history and physical examination are used for diagnosis, but the severity of the disease is determined by imaging. However, symptoms severity and structural damage assessed by imaging can be discordant; regardless of the imaging findings, in fact, each patient can present different levels of pain and functional limitation, even before any results show in radiographs.[6]

Usually, 2D radiography or computed tomography (CT) is used to image the knee. Radiography of the knee, in fact, can show osteophytes (bone spurs), subchondral sclerosis (thickening of the bone), bone attrition, and asymmetric joint-space narrowing, that give to each bone a unique shape.[1] The use of Magnetic Resonance Imaging (MRI), can reveal some of the disease manifestations even when radiography might not, thanks to its ability to visualize soft tissue.[1,4] Many different types of soft tissues are affected by OA, including cartilage, ligaments, muscle, synovium, periarticular fat, and meniscus. In OA, the complex joint mechanics gets disrupted, leading to further damage and inflammation, caused by movement and excessive loading.[6,8]

Since the joint space narrowing of the tibiofemoral joint is an important parameter to assess the severity of OA, knee radiographs should be performed in a standing position. From this 2D image, it is possible to gather information about the position of the bones under load and some information about their shape, and it can be imaged intraoperatively. X-ray can also be used to study knee kinetics. However, some types of bone shape changes are not easily visualized on 2D images, due to issues with projection, rotation and resolution, and different positioning during imaging that could mask some of the changes.[2,4]

MRI and CT scans, on the other hand, provide a 3D representation of the joint while showing information about soft tissues and bones. They can be a useful tool to inspect complex geometries without the issue of superimposition of tissues, but they have larger cost, acquisition, and computations times. They are independent of the issues of different positioning during scanning or projection effects. This type of image is made in a supine position, losing therefore information about the positioning of the bones under load. From 3D data is possible to analyse the entire joint and its modification from the physiological shape, and evaluate OA symptoms and progression.[4]

It is possible to describe the 3D image of the bones in the knee as a Statistical Shape Model (SSM). SSM are geometric models that can describe semantically similar objects as an average shape and their variation from it. In this way, the 3D object is described in a compact way. This grants not only the possibility to visualize anatomical variation from the physiological shape, but could also allow to represent disease progression.[5]

To this end, in this study different methods of building an SSM of joint will be explored, with focus on the knee joint and the joint space narrowing between the tibia and femur.

Statistical Shape Models

Statistical Shape Models: Introduction

As previously mentioned, even slight differences in shape in joint mechanics can lead to the development and progression of the disease. In order to discern physiological changes in the bone structure from non-physiological ones, we first have to define what the healthy shape of the knee joint is, and subsequently decide what constitutes a pathological change.

To some extent, the knee joint can present differences in individuals of different sex, age, height, build, and as a result of traumas, beside the normal small variations across the population.[9] To identify pathological anatomical variations, it is first needed to identify patterns in size, position, orientation, and shape in healthy subjects and define what the most common shape is. To this end, an extensive range of observations needs to be compared. Once the sample size is sufficiently large and its distribution is Gaussian, it is possible to define what the 'normal' or 'average' shape is. Each new shape presenting differences large enough from the average shape might be considered pathological.[5]

To build a statistical shape model, the first step is usually segmentation of the 3D image, followed by the definition of an object-related coordinate system and generation of a point distribution shape template, that then gets adapted to a set of objects. After that, it is possible to perform a principal component analysis and consequently a statistical analysis.

1. Segmentation

After 3D acquisition, the image is usually filtered to lower noise (e.g., noise reduction median filter) and then segmented to separate the distal femur and the proximal tibia from the surrounding soft tissue.

The segmentation method can be manual, semi-automatic, or automatic.

Manual segmentation

In manual segmentation, the shape of the object is delineated manually by an operator. It allows for individual features to be added to the model such as osteophytes[4] which can be particularly important in the study of OA knee. This method, however, is operator-dependent and time-consuming, especially in 3D images, but generally more precise compared to automatic segmentation. It is possible to calculate intra and inter-observer variability on repeated segmentation over the same image.[4,8]

Semi-Automatic segmentation

It is a form of automatic segmentation but supervised by an operator. An algorithm generates an estimation of the border of the tibia and femur, which then gets manually adjusted by an operator.[7,10] This technique substantially speeds up segmentation time.

Automatic segmentation

Automatic segmentation is a type of segmentation that is not operator dependent. Automated methods allow a more efficient way to process a large amount of data, and for this reason they are increasingly used in the latest studies.[2,11,12]

Tibia and femur have a complex shape, that can get even more complicated due to OA and its variation in shape and possible deformations such as osteophytes. Moreover, images can be influenced by noise and artifacts.

Deformable models as Active Shape Models (ASM), and Active Appearance Models (AAM) are largely used in knee OA studies. These models usually need training to be able to represent all different possibilities of shape changes in the dataset.

Active Shape Models and Active Appearance Models are both statistical modelling methods that perform feature extraction. Based on the information from the training set, statistical shape model can locate similar objects into new images, matching the model to the image more quickly compared to manual segmentation.[13–15] As a result of the ASM or AAM algorithm, we have a *statistical shape model* based on the image. From this data, it is already possible to perform statistical analysis.

To be able to perform statistical analysis on shapes is necessary to convert the geometric information of the bone shape into a discrete representation, for example sets of points or polygonal meshes. The shape is represented as a set of points distributed across the surface, which coordinates are concatenated into one single vector:

$$\boldsymbol{x} = (x_1, y_1, z_1, \dots x_n, y_n, z_n)^T \qquad\qquad Eq.\,1$$

This way of representing information about the shape's surface is also called Point Distribution Model (PDM). Additional information about connectivity is often stored to allow the reconstruction of the 3D shape. A set of points that contains connectivity information is called a *mesh*. [16]

2. Definition of an object-related coordinate system

Subsequently, a way of comparing two or more of these discrete representations is needed.[5] This presents an issue, especially since the knee joint is a combination of two bones, tibia and femur, which can present differences in shape or relative orientation and positioning. To be able to analyse the joint

only in terms of difference in shape, we need to remove all the similarity transformations from the model. We can do that by firstly determining differences in position of the bones and adding constraints to the system.

After the segmentation of the bones, in fact, either a coordinate system needs to be implemented or registration needs to be performed. The aim is to have all sets of bones in the database be represented as sets of points aligned to a common coordinate frame.[13,16,17]

These methods will be further discussed in '*Alignment of the images to the same coordinate system*' below.

3. Generation of a point distribution shape template

The models, at this point, have a large number of points, which leads to an increase in computational time and storage needed. One of the objectives of a shape model is to decrease the number of parameters needed to describe the shape of the object. Therefore, a thinning procedure over the sets of points is needed. The thinning procedure is linked with the degree of detail of the image: more detailed surfaces will need more points to describe them. Once the thinning is finished, a triangulation of the resulting point is performed.[17]

The thinning procedure is a selection of meaningful voxels within the set of surface points, the candidate set. The choice of the sub-set of points can be random or curvature guided. The algorithm iteratively picks points from the candidate set and eliminates all the points that are within a certain neighbourhood. Each surface point is assigned to a mean curvature and, starting from a selected surface voxel, all the voxels that have a surface distance less than the thinning radius decided are eliminated. The thinning radius can be constant or dependent on the surface curvature. If it is dependent on the curvature, it can be chosen to be smaller in areas with small details, and this leads to an anisotropic point distribution. In general, thinning radius defines the resolution of the distribution of points. After the thinning process, the subset of points is triangulated.[17]

4. Adaptation of the template to a set of objects

After surface thinning and triangulation, the shape is described as a set of parameter vectors. The parameter vector describing similar shapes in a dataset, however, are still not ready to be used for a statistical shape analysis: the parameter vectors would not correspond to each other. The number of surface points and triangles would be different for each shape. In order to perform a statistical analysis, the vectors need to have a one-to-one correspondence with the components of the parameter vectors. To this end, a set of landmarks should be defined in both the source and destination object. Then, the destination shape moves its surface points to resemble as much as possible the source shape, especially on the landmarks.[17]

5. Principal Component Analysis

Form the previous step, the shape is described as a set of points N, each having three components and each point represents the same shape information in each image of the dataset.

We can calculate the mean shape vector and the covariance matrix between vector elements. The principal component analysis method analyses the covariance matrix of the point distribution model, and it extrapolates eigenvalues and eigenvectors. The first principal component has the largest eigenvalue and it represents the largest variation among all the models, the second PC represents the second largest eigenvalues, and so on.

The statistical shape model then can be described by the average joint model $\bar{x}$, eigenvalues and eigenvectors.

In this way, any new shape in the dataset *x* to be approximated by the sum of the mean shape $\bar{x}$ plus the weighted sum of the principal components $\emptyset$

$$x = \bar{x} + \sum_{i=0}^{n} \omega_i \, \emptyset_i \qquad\qquad Eq. 2$$

Where n is the number of principal components needed to accurately enough explain the shapes in the datasets. Each bone will be described by *n* principal component weights ω.[4,16,18] This type of data will be used in statistical analysis.

Alignment of the images to the same coordinate system

Use of coordinate system

Prior to the modern imaging techniques, the only way to analyse the forces acting on the joints was the analysis of normal gait and experiments conducted on cadavers. The study on the gait cycle is usually non-invasive and easy to conduct but presents important limitations due to the presence of soft tissue around the bones. On the other hand, observations on cadavers can provide other types of information, but the joint is not subjected to the same forces that can be found in a living and moving patient.[19] The knee joint, being a complex system of ligaments, muscles, and different bone shapes, needs to be described in terms of joint structure and functions in mathematical terms, involving certain degrees of mechanical simplification.

After the segmentation of the bones in a dataset, it is important to bring all images in the same coordinate frame. Many examples of anatomy-based coordinate systems are present in the literature, but the one from Grood and Suntay[20] is the most used, and it is now the one recommended by the International Society of Biomechanics.[21,22] Below, three of the most famous anatomical coordinate system are described.

Morrison, 1970

Morrison[19] described the positioning of the bones as a set of references axes in relation to the tibia. It is a coordinate system in which the X axis is positive in the proximal direction, the Y axis is positive anteriorly and the X axis is positive to the right (Figure 1.a).

In this study, the condyles are simplified as a cylinder that comes in contact with a flat surface (the opposing tibial articulation) in the mediolateral direction. This line of contact is taken as the Z_g axis of the tibia, and it is considered parallel to the rotational axis of the cylinder (femoral condyles).

With an extended leg (180° extension), the axis Y_g represents the axis of rotation of the knee joint. The third axis X_g is assumed perpendicular to the other axes.

The femur is then described in terms of this system of tibial axes. The center of the femoral axes is at the intersection of the rotational axis of the femoral condyles and the Y_g axis of the tibia. The Y_f axis is represented by the mechanical axis of the femur, and the Z_f is coincident with the centreline of the condyles. Once again, the X_f axis is assumed perpendicular to the other two.

Assuming the center of the femoral axes in relation to the tibia causes a small estimation error when the knee is at full extension. Due to the non-ideal shape of the condyles, this error becomes greater with the increase of the degrees of flexion.

Extension and flexion are described along the axis Z_f, torsion along Y_g (and therefore Y_f), and adduction and abduction as redistribution of pressure along the line of contact of the condyles.[19]

Grood and Suntay, 1983

Grood and Suntay[20] introduced the Joint Coordinate System (JCS). The right-handed coordinate system describes the relative position of the tibia with respect to the femur and it is established from the position of landmarks on the bone. For both bones, the Z axis is positive in the proximal direction, the Y axis is positive anteriorly and the X axis is positive to the right (Figure 1.b).

In the tibia, the Z_g is coincident with the tibial fixed axis: it passes midway between the condyles proximally and the center of the ankle distally. It describes the internal-external rotation axis. The tibial anterior direction Y_g is the cross product of the fixed axis Z_g with a line that connects the approximate center of each plateau. The last axis of the tibial system, X_g, is completed according to the right-hand coordinate system.

The femoral fixed axis X_f is perpendicular to the femoral sagittal plane, positioned through both femoral epicondyles. It consists of a medial-lateral axis, along which extension and flexion occur.

The mechanical axis Z_f connects the femoral head and the point between the condyles, in the most distal point on the posterior surface. The femoral anterior (Y_f) is obtained from the cross product of the mechanical axis Z_f and the line connecting the two points on the posterior surface of the femoral condyles.

Along the floating axis perpendicular to both the femoral fixed axis and the tibial fixed axis adduction and abduction occurs.[8,23]

Pennock and Clark, 1990

In this study Pennock and Clark[24] stated that a realistic representation of the knee joint would be a six-link open-chain connected by three prismatic joints and three revolute joints, however, a three cylindric open chain is proposed as a good compromise to avoid numerical solutions. In this study too, anatomical landmarks are used to define the coordinate system, although it is declared that the solution proposed by Grood and Suntay can be deduced as a special case from this coordinate system (Figure 1.c).

The method proposed in this study has the origin of the femoral frame positioned in the middle of the two condyles, on the trans-epicondylar line. It is along this line that the x axis of the femur X_f is. By drawing an imaginary line that connects the origin of the femoral frame and the center of the femoral head and crossing it with the trans-epicondylar line, the y axis Y_f is defined, directed anteriorly. The third axis X_f consists in the cross product of the other two axes.

The origin of the tibial coordinate system, instead, can be found at the proximal tip of the medial spine of the tibial eminence. Directed proximally, the z axis Z_g connects the origin to the center of the ankle. The x axis X_g on the tibial frame is perpendicular to Z_g and it is parallel to the line that crosses the centers of the tibial condyles. Finally, Y_g is the cross-product of the other two axes, X_g and $Z_{g.}$

In this system, the six displacements can be described with the three-cylindric open chain. Flexion and extension and medial-lateral shift are about and along the trans-epicondylar line. Adduction and abduction, anterior and posterior drawer are along and about the floating axis whereas internal and external rotation and compression and distraction are about and along the tibial z axis.

Examples of studies using the coordinate system in relation to knee OA

Already in a study from 1989, Hutton et al.[25] described how bony changes appear in osteoarthritic joints can appear years before the ones in the cartilage, opening the possibility to treat the knee with different therapies before more sever join damage would occur. At the time, the study was made only on 2D x-ray images and the authors were well aware of the limitations that that implied.

In 2010, Bredbenner et al.[7], decided to test that hypothesis using more technologically advanced tools: MRI scanning and statistical shape models. In this way, the 3D images from MRI were filtered and segmented using a semi-automatic tool to isolate the tibia and femur, then a triangulate surface was created on the bone. The triangulated surface of each bone was then analysed through principal component analysis. Then the model was aligned using Grood and Suntay's[20] coordinate system. From this analysis, differences in bone shape between subjects at risk of developing OA and healthy subjects were demonstrated in non-weight-bearing conditions, and their magnitude was measured using SSM.

In 2019, Lynch et al.[4] explored 3D regional anatomical differences in osteoarthritic knees, indicating which types of changes in the shape of the whole joint subchondral bone could be used as a possible biomarker to distinguish between healthy and diseased knee joints. In fact, Bredbenner et al.[7] observed changes in shape before symptoms develop, and other authors identified which bone shapes are most common in already symptomatic OA knee (Neogi et al.[2], Barr et al.[12]). In this study, tibia and femur were segmented from CT images, then the three-dimensional coordinate system defined by Grood and Suntay[20] was established. The 3D models were exported as meshed surfaces, the principal component analysis was run firstly using the mesh of one of the knees in the dataset as a model, then using the average shape resulted in the previous step as a model itself. In this way, it was observed expansion of the cartilage plates up to 190 development of the tibial tubercle up to 115%, and other changes.
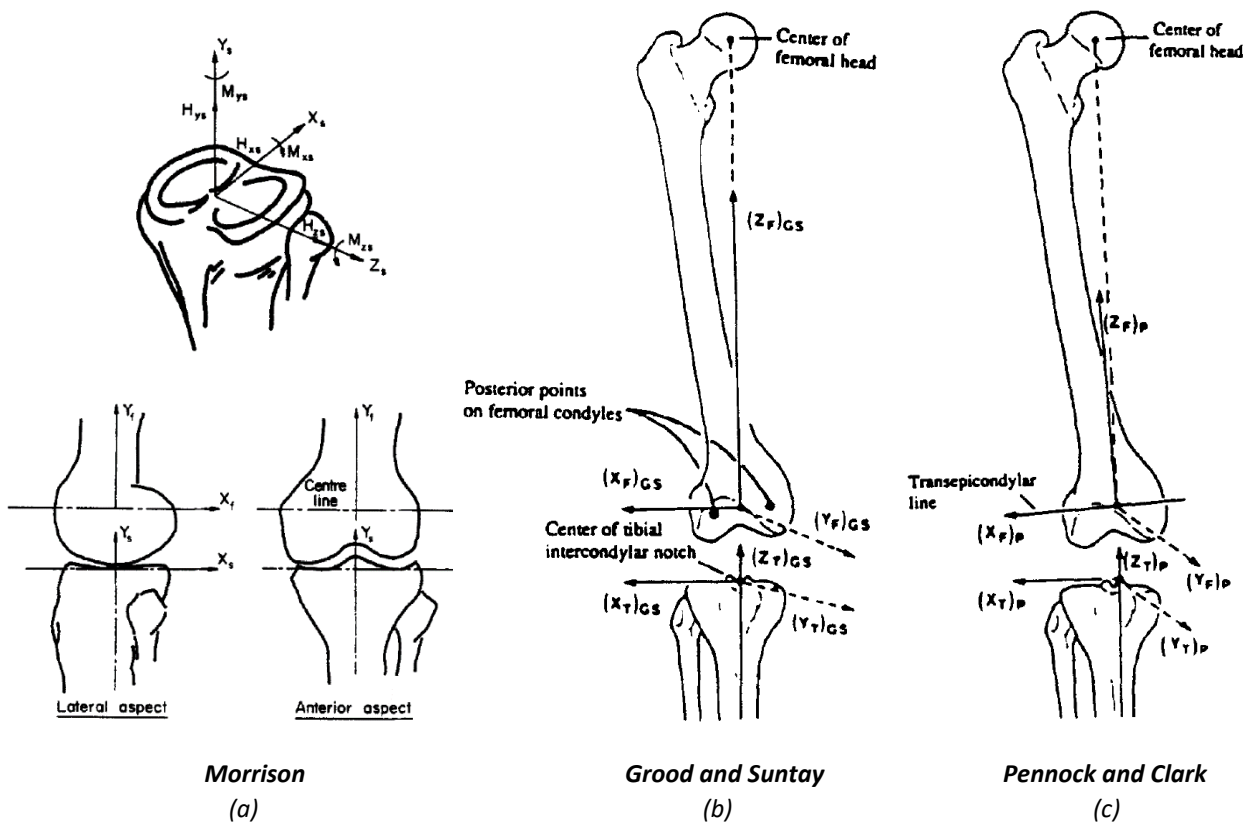

Morrison
(a)

Grood and Suntay
(b)

Pennock and Clark
(c)

Figure 1 *Representation of anatomical coordinate systems. (a) Morrison (b) Grood and Suntay (c) Pennock and Clark. Sources: [19,24,24]*

Use of registration

One of the many uses of registration is interventional radiology, used to bring pre-interventional and intra-interventional data in the same coordinate frame. The pre-interventional data is usually a 3D representation of the patient's anatomy as MRI or CT, whereas the intra-intervention data are patient's images that can be in 2D (ultrasound, projective x-ray as fluoroscopy, CT-fluoroscopy and optical images) or 3D (for example cone-beam CT or ultrasound or 3D models of the object).[26]

We can then have a combination of registration of those two types of medical images: either 3D-3D, 2D-3D, 3D-2D, or more rarely now 2D-2D. The result is often a 3D model, from which is possible to measure the dimension of the bones and the gaps between them and quantify misalignments or distribution of forces.

Registration algorithm

The registration algorithm could be summarized in four parts: feature extraction, feature matching, transform model estimation, image resampling, and transformation.

In *feature extraction*, the contour of the object to be registered is extracted from the background. In the *feature* matching phase, corresponding features between the two images are aligned. Many features descriptor or similarity measures can be used for this purpose. During the *transform model estimation*, mapping functions are created as a consequence of the feature correspondence used. In *imaging resampling and transformation,* the image is transformed depending on the mapping functions. The values in the image that are not represented as integer coordinates are then computed by interpolation.[27]

In 1998 Maintz and Viergever[28], proposed a way to classify different image registration methods based on 9 categories. Among the most important, we will discuss:

- Image modality
- Image dimensionality
- Nature of the registration basis

Image modality

Depending on the imaging modality involved, the registration between image types can be multi-modal, quasi-intra-modal, or model to modality.

In multi-modal image registrations, distinct types of images are registered together. An example could be MRI for the 3D data and x-ray imaging for the 2D. For quasi-intra-model similar image types are used, for example, CT and x-ray imaging: in principle, they work in the same way, but they use different detectors and photon energies and, as a consequence, they might present differences in intensities. Since they use similar technologies, they will be easier to register together compared to multi-modal images. In model to modality, a 3D statistical or geometrical model is registered to a 2D or 3D image.[26]

Nature of the registration basis

Registration can either be extrinsic or intrinsic. In case of extrinsic registration, fiducial markers are used. Skin marker-based methods such as stereophotogrammetry are used in clinic, especially for measurements of 3D kinematics. Due to skin movement artifacts, however, they do not present accurate enough results. Utilizing intracortical bone pins can produce results of higher quality, but they are excessively invasive for the patient. They expose the subject to the risk of infections and can also interfere with their usual kinematics.[29]

On the other hand, intrinsic methods solely rely on images of anatomical structures. They can be furtherly classified as feature-based, intensity-based, and gradient-based.

In *feature-based* registrations, the aim is to find a transformation that minimizes the distances between corresponding features in the two images. For this reason, the accuracy of this method is highly dependent on the quality of the segmentation. The simplest feature-based registration method is the *point-to-point registration*, in which landmarks from the two images have to be aligned. This presents some difficulties, especially if the registration is between 2D and 3D data: points that can easily be found in 3D images might be difficult to individuate in 2D images. Since this method is too dependent on the skill of the user, it is usually used as a rough initial registration, after which more sophisticated methods are used.[26] By using methods such as *curve-to-curve* or *surface-to-curve*, the problem mentioned is avoided. Correspondence between curves and/or points is typically obtained by finding the minimal Euclidean distance between features. The algorithm for the registration is seen as an iterative procedure that alternates steps of correspondence (in which the distance between the features is quantified) and transformation steps (in which the position of the data changes to be more similar to the source image).[26]

Another way to register an image depending on its feature is to use a library-based registration. The image is registered to a template, serving usually as a coarse registration used for initialization. It is important to remember that the feature-based registrations are solely based on surface information, and do not have any information about the internal structure of the bone.[30]

In contrast, *intensity-based* methods transform the image based on the intensity values of voxels and pixels. Instead of using distance, similarity measures based on voxel and pixel-wise comparison are used.[30,31] Contrary to feature-based methods, intensity-based registrations do not need segmentation of the images.

The *gradient-based* registration method was introduced by Tomasevic et al.[32] and Livyatan et al.[33] in 2003. It uses volume gradients on edge pixels of x-ray images to eliminate outliers or foreign objects. Compared to other methods, it has lower computation times, higher accuracy, and robustness.

Image dimensionality

In order to perform registration between 2D and 3D images, there is the need to either transform the 2D data into 3D data or vice versa. The result is therefore a 2D or a 3D image.

To reduce the dimensionality of a 3D image, it can be *projected* to 2D images. To increase the dimensionality of a set of 2D images, instead, *back-projection* can be used. With *reconstruction*, it is possible to reconstruct 3D data based on 2D images. While in projection or back-projection one 2D image could be enough to achieve the registration, in case of registration at least two 2D images are required (more images will increase the accuracy and quality of the model).[26] Figure 2 perfectly shows the different combinations of image dimensionality and nature of the registration basis.

3D/3D registration to 3D model

In this type of registration, a 3D image can be registered to another 3D model, for example an atlas. This method is often used for the creation of statistical shape models. It can also be used in cases of multi-modal 3D images, where images from CT scan and MRI are registered together, to gather information about soft tissue from the CT scan and about the bone morphology from MRI. An example of this technique is used by Ciliberti et al.[34], with the aim to assess the link between cartilage health and OA in the knee.

3D/2D registration to 2D model

To perform this type of registration, the 3D data has to be projected into bi-dimensional planes. The projection of the 3D model on the 2D plane is then registered with the 2D image and the result is a 2D image.

This type of registration can be feature-based, where the aim is to minimise the distance between the projected 3D contour and the 2D image, intensity-based where the 2D image is registered to a 2d Digitally Reconstructed Radiograph (DRR), or gradient-based when there is an optimization of the similarity measure between the projected 3D gradient vector and the 2D gradients.[26]

A highly accurate way to approach 3D modelling of joint component kinematics is Roentgen Stereo Analysis (RSA). With this method, tantalum beads are implanted into the bones during surgery and by using x-ray images a 3D model is created. Needless to say, this procedure, which has to be performed under general anaesthesia, is invasive. In an alternative approach proposed by Tashman et al.[35] in 1995, the 3D CT data from a bone combined with the information from 2D simultaneous images (fluoroscopy) could be used to create a 3D model of the bone non-invasively. This method, however, requires more radiation compared to the previous one and the field of view obtainable is rather small.

For this reason, new methods have been proposed, in which a single-plane fluoroscopy image can be combined with the 3D data. In this way, the subject has more freedom of movement while being scanned and receives fewer radiations.

Hossain et al.[36] in 2013 proposed a 3D-2D registration algorithm to register 3D data to 2D single-plane fluoroscopy frame for knee joints after Total Knee Arthroplasty (TSA). In this method, the similarity measure proposed is the sum of conditional variances (SCV), which as a result gives a number indicating how well the two sets of information are aligned. The optimization aims to determine the value for a set of parameters describing the 6 movements (3 translations and 3 rotations) that will enable the best agreement between the 2D target image and the 2D image generated from the 3D object.

In order to do that, we first have to introduce the concept of Digitally Reconstructed Radiograph (DRR). It is a way to reduce a 3D volume to a 2D image. It is generated by simulating the passage of x-rays through the bone, calculating the cumulative attenuation of the ray as it passes through the various voxels.

In this method, at every iteration of the registration algorithm, the 3D rigid-body geometric transform is applied to produce a change of position of the 3D model. Then the volume is reduced to a DRR, and the similarity measure is calculated. The resulting gradients are used to determine in which way the 3D model has to move in the next iteration. The algorithm is repeated until the parameters found are satisfactory.

In 2010, Tsai et al.[29] proposed a similar method, but for natural knee joints and for in vivo kinematics. In this study, the similarity measure used is called the weighted edge-matching score (WEMS). It is to be noted how natural bones differ from Total Knee Replacement (TKR) components in form and internal structure and how this difference is also reflected in fluoroscopic images. In this case, the challenge would be having less-defined edges to contour. Methods using bi-planar fluoroscopy[37,38] have been proposed. Despite being more accurate, using bi-planar fluoroscopy instead of single-plane increase the radiation dose on the patient and, in some cases, necessitate the surgical implantation of metal beads, restricting the use of this method to a limited population.[37]

2D/3D registration to 3D model

In this type of registration, a series of 2D images are used to reconstruct a 3D model of the image. This model is then registered to another 3D model, resulting in a 3D model.

The feature-based version of this type of registration simply minimises the difference between the reconstructed and original 3D sets of points representing the models. In the intensity-based method,

a series of 2D radiographs are reconstructed into a 3D model, which then is registered to a 3D image using some similarity measure. In the gradient-based version, instead, the 2D gradient images are reconstructed into a 3D gradient vector field, that it is then registered to a 3D gradient vector optimizing similarity measures.[26]

The first instances of this technique are from Banks and Hodge[39] and Hoff et al.[40], in 1996. It originates from the need to create a technique able to measure knee kinematics patients after TKR. Markers on the skin were proven not to be extremely accurate to represent bone motion and attaching markers to the bone too risky for the health of the subject and extremely invasive. High-speed CT and MRI did not have the capacity to obtain a full 3D scan of the joint during dynamic activities and additionally, they presented some issues due to the large metallic implants in the bone caused by TKR. Moreover, they are limited to static and non-weight-bearing conditions. For these reasons, Banks and Hodge proposed a way to measure the 3D kinematics of a joint after TKR during dynamic activities using x-ray fluoroscopy. In this way, the use of a set of 2D images (minimum of two) can be used to create a 3D model.

Using x-ray fluoroscopy, the joint is scanned as a set of 2D images. The edges of the *prosthesis* are then extracted and compared with the precomputed contours of a geometric model of the prosthesis. At this point, knowing the position and orientation of the computer model that generated the best matching contour allows estimating the position and orientation of the prosthesis and consequently of the bone.[39,40] More recently, however, other studies have improved this technique by developing a full 6 degree of freedom kinematic analysis, also improving the accuracy of the depth position.[41]

Many other authors proposed this method to create 3D models, for example Hosseini et al.[42], that used it to measure the real-time tibiofemoral cartilage contact deformation and area under load. They used two orthogonal fluoroscopes to acquire a set of 2D images, from which a 3D model was created (virtual DFIS). The 3D model from MRI was also imported in the virtual DFIS, viewed from the same two orthogonal directions corresponding to the fluoroscopes. Then the knee model was manually translated and rotated until the projection of the model matched the outlines of the corresponding bones on the imported images. Once the model was in the right position, additional information on cartilages was uploaded and checked at each time point. Similarly, Sharma et al.[43] studied tibiofemoral cartilage deformation as a possible biomarker for knee osteoarthritis. They proposed a marker-based and markerless approach to achieve that. The marker-based method only used 2D dual fluoroscopy images in various positions, whereas the markerless also used information from CT scans. Kanhonou et al.[44], instead, aimed to investigate kinematic or postural differences between healthy and pathological populations.

In 2020, Postolka et al.[30] investigated the accuracy, reliability, and repeatability of an intensity-based 2D/3D algorithm using a calibration object mounted on an artificial femur and tibia. Volumetric models were acquired using CT scans, while each bone was imaged statically and dynamically using videofluoroscopic imaging. The 3D volume from the CT was firstly manually manipulated such that the projection of the bone surface models optically matched the fluoroscopic image, then those poses were used as initial poses for registration for the intensity-based registration algorithm. As a result, they suggested that an approach that includes manual intervention could be key for efficient and accurate registration.

Finally, in 2021, Wang et al.[45] proposed a deep-learning method to measure in-vivo knee joint motion. Machine learning used to measure joint kinematics is computationally efficient and permits an enhanced capture range compared with optimization-based methods but necessitates a considerable amount of images. For simplicity, DDRs are typically used for training, but they also require a large

number of authentic images to ensure robustness. DDRs, in fact, present sharper edges compared to authentic x-ray images and do not usually have geometric distortion or issues with nonuniform intensity. To overcome the limitation of the number of real fluoroscopic images, the authors developed a method that combines the pseudo-Siamese point-tracking network with a feature-transfer network. This approach can decrease the demand for real x-ray images thanks to the ability to transfer authentic features to synthetic images. Analogously to other learning-based strategies, however, the resulting accuracy is not high, but much faster compared to other optimization-based methods. For this reason, the authors proposed that this method could be used as an initialization step for the optimization-based registration method to improve accuracy.

2D/3D registration to 3D model

Using back-projection, information from a 2D image is used to modify a 3D model. It can be either feature-based, where the aim is to minimise the distance between the occluding contour and the virtual ray from the 2D image or gradient-based, where a similar process happens, but by optimising the similarity between the 3D gradient vector and the back-projected 2D gradient vectors.[26]
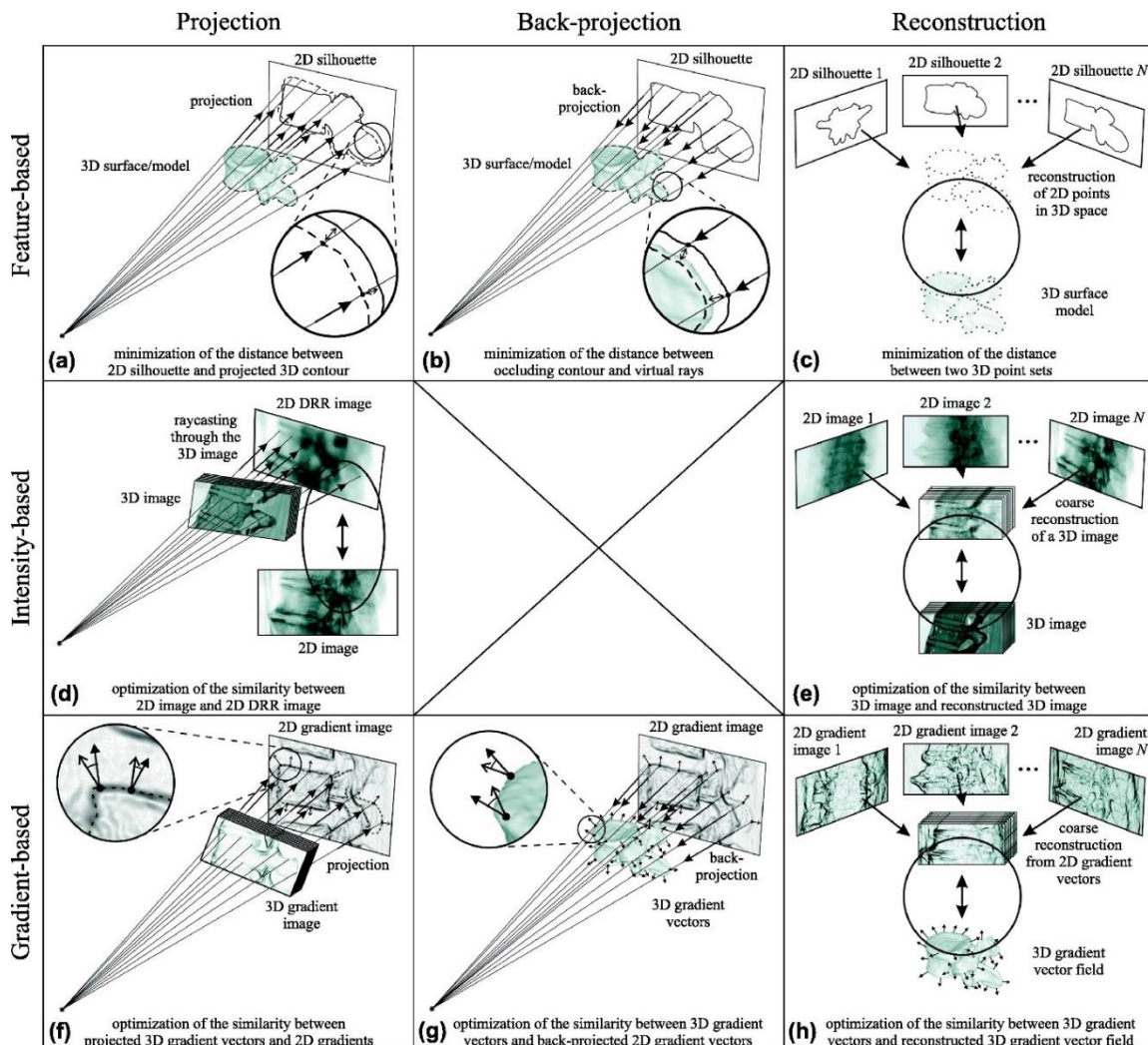

Figure 2 *Different types of registration based on image dimensionality and nature of the registration basis. Source: Markelj et al. [26]*

Articulated SSM

Articulated Statistical Shape Model (ASSM) is an extension of conventional statistical shape models. SSM is used to combine information about shape variability of the anatomical objects in a dataset, while ASSM also adds information about the physical variation of pose between the same objects. As previously mentioned, knowledge about joint posture and relative positionings adds robustness to the model. In order to do that, Bindernagel et al.[46] proposed a pipeline for the knee joint that incorporates statistical shape variation to explicit degrees of freedom that model the physiological joint motion. The joint model consists of the tibia and femur, and the joint motion proposed is a rotation along the epicondylar axis and a transition. In this model, one bone is considered fixed and the other mobile, in fact, the transformations are described for the tibia relative to the femur. The MRI images are segmented, and a 3D model is constructed; landmarks are added to the model and those landmarks are then aligned with all the other images in the dataset, to have all the 3D sets of points in the same coordinate system. The object is usually aligned via rigid and scale transformation. In contrast to SSM, ASSM requires additional alignment via transformations according to the joint model. Finally, PCA is performed over the meshes. This method proved that both SSM and ASSM performed similarly on the femur, but the reconstruction quality of the tibia was superior using ASSM. For this reason, the authors believe that ASSM could be a promising tool to reconstruct anatomical structure from images that present low contrast or from subjects with pathologies.[46]

Conclusion

This manuscript presents, to the best of the author's knowledge, an extensive review describing different ways to represent the knee joint and the creation of statistical shape models, with a particular focus on knees affected by osteoarthritis. In the creation of a SSM, the alignment of sets of points to the same coordinate system is needed. Two main ways to achieve that have been described: the use of a coordinate system and registration.

The use of a coordinate system only necessitates one type of 3D image (CT or MRI). In the three systems of coordinates proposed, one bone is considered fixed (the femur) and the other one is moving (the tibia) therefore the alignment of the bones relies entirely on the chosen coordinate system. In this way, however, an important piece of information is lost: the relative position of the bones with each other under load. The joint, being a complex structure, needs to be represented in the most complete way possible to have a clear overview of the severity of the disease.

For this reason, registration using images from different modalities could be a way to represent the knee joint with more completeness. It requires more computational time and often training but represents a faster way to analyse large amount of data. It is also independent from the skill of the operator, and its results are consistent in time. As for now, it requires the patient to be scanned with two different imaging techniques, potentially increasing radiation levels, however the resulting model is an accurate representation of the knee joint. By gathering information from 3D data (that better represents complex shapes) and 2D data (that can give information about kinetic or bone positioning under load), the resulting 3D model can represent more accurately the joint under load and it could be possible to introduce information about the soft tissues to it. This method could help better represent all the differences in bone shape and soft tissues deformation that can be used as a biomarker to better diagnosticate osteoarthritis, identify at-risk subjects, and improve the development and testing of treatments.[2,7]

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