Review

Machine learning in knee osteoarthritis: A review

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\textbf{Keywords:} & \textbf{SUMMARY} \\
Knee osteoarthritis & Objective: The purpose of present review paper is to introduce the reader to key directions of Machine Learning techniques on the diagnosis and predictions of knee osteoarthritis. \\
Feature engineering & Design: This survey was based on research articles published between 2006 and 2019. The articles were divided into four categories, namely (i) predictions/regression, (ii) classification, (iii) optimum post-treatment planning techniques and (iv) segmentation. The grouping was based on the application domain of each study. \\
Machine learning & Results: The survey findings are reported outlining the main characteristics of the proposed learning algorithms, the application domains, the data sources investigated and the quality of the results. \\
Prediction & Conclusions: Knee osteoarthritis is a big data problem in terms of data complexity, heterogeneity and size as it has been commonly considered in the literature. Machine Learning has attracted significant interest from the scientific community to cope with the aforementioned challenges and thus lead to new automated pre- or post-treatment solutions that utilize data from the greatest possible variety of sources. \\
Classification & \\
Segmentation & \\
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1. Introduction

Knee Osteoarthritis (KOA) is a degenerative disease of the knee joint and the most common form of arthritis causing pain, mobility limitation, affecting independence and quality of life in millions of people \cite{1}. There is no known cure for KOA, but there are several medical, biological and environmental risk factors, both modifiable and non-modifiable, that are known to be involved in the development and progression of the disease \cite{2}. The aforementioned data characterizing KOA are high-dimensional, heterogeneous and the limited number of simple logistic regression models are not capable of handling large numbers of risk factors and most importantly, any interactions between environmental and other medical and biological factors. Furthermore, they cannot identify the tendency of a healthy subject to show signs of the disease and its progression based on patient outcomes. Despite that, the power and importance of correct study design should not be underestimated. In the well-designed study even “simple” analysis can give trustworthy results. These significant shortfalls in OA risk prediction models require a completely different modeling and computational approach to the problem. Advanced machine learning techniques such as fuzzy-logic theory, discrimination metrics (e.g. mutual information gain indexes and Fisher discrimination ratios) and advanced classification models combined with novel and efficient feature selection methods suitable for very large data sets could significantly contribute to the problem of high dimensionality compared to the existing statistical techniques applied to the OA risk prediction problem.

Machine Learning (ML) is the study of how computer algorithms (i.e., machines) can “learn” complex relationships or patterns from empirical data and hence, produce (mathematical) models linking an even large number of covariates to some target variable of interest \cite{3}. As mentioned before, the ability to analyze complex cases with a huge volume of data and the maximum possible results it renders ML a valuable tool against KOA. It is worth noting that ML has been applied in areas such as robotics \cite{4}, medicine \cite{5}, biochemistry \cite{6}, bioinformatics \cite{7}, meteorology \cite{8}, agriculture \cite{9} and the economic sciences \cite{10}. The importance of applying ML techniques to KOA has been documented by Jamshidi et al. \cite{11} and Kluzek and Mattei \cite{12} in 2019.

In this context this review has been carried out to allow each researcher to refer to the appropriate ML method in relation to KOA. To achieve this aim, the structure of the review is as follows. Section 2 \textit{Machine Learning in a nutshell} presents the terminology and definitions, the types, tasks and models, which are used in the studies on which this review was based. Section 3 \textit{Review of studies} presents the steps of the methodology that were followed for the collection and classification of the studies concerning ML techniques in KOA. In addition, it presents a

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summary of the studied literature, highlighting the main characteristics of proposed ML approaches divided into four categories. The review ends with Section 4 Discussion and Conclusions, which mentions the future expectations and advantages that exist through the usage of machine learning in knee osteoarthritis.

1.1. Machine learning in a nutshell

In ML, a sample (e.g. a patient) is represented by a number of features which come in various forms and formats including patient's characteristics, risk factors, shape/texture characteristics in medical images or clinical history data. To facilitate the learning process, there features are typically concatenated forming a multidimensional feature vector. ML systems (Fig. 1) operate in two phases: the learning phase (training) and testing one. Indicatively, the role of the pre-processing unit can be improved. The feedback loop allows adjustments of the pre-processing and feature extraction/selection units that will further improve the performance of the learning model. During the testing phase, the trained model is shown previously unseen samples (represented as images or feature vectors) that need to be classified. The model makes an appropriate decision (classification or regression) based on the features that are present in each sample. Deep learning [14], that is a subfield of machine learning concerned with algorithms inspired by the structure and function of the brain, sets an alternative architecture by shifting the burden of feature engineering (the process of transforming raw data into features) to the underlying learning system. From this perspective, feature extraction or selection are omitted leading to a fully trainable

![Image](https://via.placeholder.com/150)

**Fig. 1.** A typical machine learning system.

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| Category          | Models                                                                 | Description                                                                 | Advantages                                                                 | Disadvantages                                           |
|-------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------|
| Bayesian          | Naive Bayes, Gaussian Naive Bayes, Multinomial Naive Bayes, Bayesian    | Probabilistic graphical models in which the analysis is undertaken within the context of Bayesian inference | They model uncertainty; easy to handle missing and hidden data             | Increased computational cost in high-dimensional spaces; they require subjective definition of prior probabilities |
|                   | Belief Network [29–32]                                                 |                                                                             |                                                                           |                                                         |
| Linear            | Linear regression [17,18]                                              | The best fit line through all data points                                    | Easy to understand and implement; models can be easily interpreted      |                                                          |
|                   | Logistic regression [17]                                               | The adaptation of linear regression in classification problems              |                                                                           |                                                          |
|                   | Decision trees (DT) [37–39]                                            | A decision support tool that uses a tree-like graph or model of decisions and their possible consequences, including chance event outcomes, resource costs, and utility |                                                                           | Not powerful enough in problems of high complexity       |
| Tree-based        | Random forest (RF) [33]                                               | Ensemble model that produces multiple decision trees, using a randomly selected subset of training samples and variables. | Fast to train and powerful                                               | Not so interpretable; slower than other techniques       |
|                   | Gradient boosting [40]                                                | Uses weak decision trees as base models. Predictive results are obtained through increasingly refined approximations. | Fast and high performing                                                  | Interpretability issues; sensitive to small changes     |
| Neural networks   | Neural networks [41–50]                                                | Information processing paradigm that is inspired by the way biological nervous systems, such as the brain, process information. | Can handle complex problems                                              | Not interpretable; slow                                |
|                   | Deep Neural networks (DNN) [51] such as CNN [52], deep belief network  |                                                                              |                                                                           |                                                         |
|                   | [53], and auto-encoders [54].                                          |                                                                             |                                                                           |                                                         |
| Instance based    | K-Nearest Neighbor [55], Locally Weighted Learning [56], Learning      | Memory-based techniques that learn by comparing new examples with instances in the training database | Simple and fast to implement                                             | Complexity grows with data (up to O(n) where n is the number of the training examples), prone to overfitting |
| models            | Vector Quantization algorithm [57], Self-Organising Maps [58]          |                                                                             |                                                                           |                                                         |
| Support vector    | SVM [59,60]                                                             | Finds a solution (linear or non-linear) that maximizes the margin between classes | SoA performance; generalized solutions; robust to high dimensionality     | Tuning hyperparameters is crucial; time consuming and difficult to interpret |
| machines (SVMs)   | Least Squares SVM [61]                                                 |                                                                             |                                                                           |                                                         |
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system that begins from raw or pre-processed input (e.g. image pixels or time-series) and ends with the final output of recognized objects or predicted values.

Learning can be classified as supervised, unsupervised or reinforcement learning. In supervised learning, each data sample is represented by a pair consisting of an input (typically a multi-dimensional feature vector) and a desired output value (e.g. a label having real-world meaning such as Kellgren Lawrence grades in case of KOA). The training phase involves the task of learning a function that maps every input to its associated output. It is usually performed prior to applying a classification or regression model in order to avoid the effects of the curse of dimensionality. Some of the most common DR algorithms are the following: (i) principal component analysis (PCA) [22], (ii) partial least squares (PLS) regression [23] and (iii) linear discriminant analysis (LDA) [24]. Finally, clustering [25] is an application of unsupervised learning typically used to find natural groupings of data (clusters). Well established clustering techniques are the K-means technique [26] hierarchical clustering [27], and the expectation-maximization technique [28].

Recently, deep learning has attracted wide-spread attention because of its enormous representing power, automated feature learning capability and best-in-class performance in solving complex problems [62]. Deep NNs make use of deeper architectures, extensible hidden units and nonlinear activation functions to model complex data, whereas one of variables which are known. The most known regression algorithms are the linear regression [17], as well as, stepwise regression [18]. Also, more complex regression algorithms have been developed, such as ordinary least squares regression [19], multivariate adaptive regression splines [20], multiple linear regression, and locally estimated scatterplot smoothing [21]. Table 1 cites the most well-known state-of-the-art ML models of the literature. Dimensionality reduction (DR) is a task that belongs in both families of supervised and unsupervised learning types, with the aim of providing a more compact lower-dimensional representation of a dataset preserving as much information as possible from the original data. It is usually performed prior to applying a classification or regression model in order to avoid the effects of the curse of dimensionality. Some of the most common DR algorithms are the following: (i) principal component analysis (PCA) [22], (ii) partial least squares (PLS) regression [23] and (iii) linear discriminant analysis (LDA) [24]. Finally, clustering [25] is an application of unsupervised learning typically used to find natural groupings of data (clusters). Well established clustering techniques are the K-means technique [26] hierarchical clustering [27], and the expectation-maximization technique [28].
their most attractive aspects is that they automate feature engineering thus alleviating the need for domain expertise and hardcore feature extraction. Currently, DL models have dramatically improved the state-of-the-art in many different sectors and industries including healthcare [63]. DL models can be either supervised, partially supervised, or even unsupervised. Convolutional neural networks (CNN) are among the most famous DL networks where feature maps are extracted by performing convolutions in the image domain. A comprehensive introduction on CNNs is given in Refs. [52]. Other typical DL architectures that belong to the family of probabilistic undirected graphical models are deep Boltzmann machines, and deep belief networks [53].

Auto-encoders [54] are unsupervised DNNs whose main idea is to encode high dimensional data into a low-dimensional latent vector and try to reconstruct the input data as flawlessly as possible by only using its

### Table 3

| Author                | Year | Data                              | Feature engineering | Learning Algorithm                  | Validation | Results.          |
|-----------------------|------|-----------------------------------|---------------------|--------------------------------------|------------|-------------------|
| Alsehiri, O           | 2013 | Demographic characteristics and some gene polymorphisms | SVM, PNN           | 152 OA knees for training and 102 healthy for testing | 76.77% acc & 90.55% acc |
| Beynon, M. J.         | 2006 | Biomechanical Data                | Simulated annealing (SA) and genetic algorithms (GAs) | Dempster-Shafer theory of evidence (DST) & Linear discriminant analysis (LDA) | LOOCV      | 96.7% & 93.3% acc |
| de Dieu Uwisengeyimana, J | 2017 | Biomechanical Data                | Time-domain statistical features | Multilayer perceptron, Quadratic support vector machine, complex tree & deep learning network with k-NN | 22 subjects (11 healthy and 11 OA) | 99.5%, 99.4%, 98.3% & 91.3% acc |
| Deluzio, K.J.         | 2007 | Biomechanical Data                | PCA                 | Discriminant analysis                | CV         | Misclassification rate 8% |
| Jones, L.             | 2008 | Biomechanical Data                | PCA                 | The Dempster-Shafer (DS)–based classifier & ANN | LOOCV      | 97.62% & 77.82% acc |
| Kotti, M.             | 2014 | Biomechanical data                | PPCA                | Bayes classifier                      | 47F-CV     | 82.62% acc         |
| Kotti, M.             | 2017 | Biomechanical data                | –                   | Random forest                        | 50% training/50% testing, 5F-CV | 72.61% acc |
| Lim J.                | 2019 | Demographic and personal characteristics, lifestyle- and health status-related variables | PCA                 | DNN                                  | 66% training/34% testing | AUC of 76.8% |
| Long, M. J.           | 2017 | Outcome scores and biomechanical gait parameters | –                   | KNN                                  | 70% training/30% test. 30% of training was left out for validation | AUC of 1.00 |
| McBride, J.           | 2011 | Biomechanical data                | –                   | Neural networks                      | 50% training/50% testing | 75.3% acc       |
| Mezhghani, N.         | 2008 | Biomechanical data                | –                   | Nearest neighbor classification (NNC) | 38 of 42 cases acc | 91% acc         |
| Mezhghani, N.         | 2008 | Biomechanical data                | –                   | Nearest neighbor classification (NNC) | LOOCV      | 67% acc         |
| Mezhghani N.          | 2017 | Biomechanical Data                | –                   | Regression tree                      | 10F-CV     | ROC AUC of 0.85   |
| Moustakidis, S.       | 2010 | Biomechanical data                | Wavelet Packet, FS via SVMFuzCoC | KNN1 SVM (AAA) SVM (1AA) FCT G4 FDT-SVM | 10F-CV     | 86.09% acc 89.71% acc 90.18% acc 88.35% acc 91.12% acc 93.44% acc |
| Moustakidis, S.       | 2019 | Clinical Data                     | Feature subsets exploration | DNN Adaboost Fuzzy RNN Fuzzy NPC CFKNN | 10F-CV     | 86.95% acc (for age 70+) 78.60% acc 77.39% acc 72.40% acc 73.60% acc 98–100% acc |
| Phinymark, A.         | 2016 | Biomechanical Data                | PCA                 | SVM                                  | 10F-CV     | 1.5 of the subjects has been misclassified 80% acc |
| Şen Köktas, N.        | 2006 | Biomechanical data                | –                   | MLPs                                 | CV         | 1.5 of the subjects has been misclassified 80% acc |
| Şen Köktas, N.        | 2010 | Biomechanical data (Also included age, body mass index and pain level) | Mahalanobis Distance algorithm | Decision tree - MLP multi-classifier | 10F-CV     | 66.7% training/33.3% validation, KNHANES V-1 (internal validation group) and OA (external validation group) |
| Yoo, T. K.            | 2016 | Predictors of the scoring system in the Fifth Korea National Health and Nutrition Examination Surveys (KNHANES V-1) data | Logistic regression | ANN                                  |            | ROC AUC of 0.66–0.88 |
| Author                  | Year | Data                  | Localization of joints | Feature engineering | Learning Algorithm | Validation | Results               |
|------------------------|------|-----------------------|------------------------|---------------------|-------------------|------------|-----------------------|
| Bien, N.               | 2018 | MRI                   | –                      | –                   | CNN (MRNet)       | Validation A: 82.9% training, 8.5% tuning and 8.6% validation B: 60%-20%-20% into training, tuning, and validation sets using an external dataset | AUC of 0.937 |
| En, Chuah Zhi          | 2013 | MRI                   | –                      | Discrete Wavelet Transform (DWT) | ANN-based         | 57.1% (200 images) training/42.9% testing (150 images) | 94.67% acc |
| Kubkaddi, Sanjeevakumar | 2017 | MRI                   | –                      | GLCM                | SVM with RBF kernel, SVM with linear kernel & SVM with polynomial kernel | 70% training/30% testing | 95.45% acc, 95.45% acc & 87.8% acc |
| Kumarv, A.             | 2017 | MRI                   | –                      | GLCM                | PLS with forward feature selection (PLS-FFS) | Fisher LDA, PLS regression, sparse PLS and sparse LDA | 10F CV |
| Marques, J.            | 2012 | MRI                   | –                      | GLCM                | Densely Connected Convolutional Neural Network (DenseNet) | 65-20-15% split of training, validation, and holdout testing set |_ACC of 0.937 |
| Pedoia, V.             | 2019 | X-ray (T2 relaxation time maps), Demographics and KOOS | –                      | PCA                 | Self Organising Maps (SOM) | 16.2% training/83.8% testing | Accuracy rate of 93.8% for KL-Grade 0, 70% for KL-Grade 1, 4% for KL-Grade 2, 10% for KL-Grade 3 and 88.9% for KL-Grade 4 |
| Anifah, L.             | 2013 | X-ray                 | Gabor filter           | GLCM                | Multi-class classification accuracy | 60.3% |
| Antony, J.             | 2017 | X-ray                 | FCN                    | FCN                 | CNN                | Multi-center validation | Multi-class classification accuracy |
| Antony, J.             | 2016 | X-ray                 | Sobel horizontal image gradients, linear SVM | Pre-trained CNN (BYLC reference CaffeNet and VGG-M128 networks) | Linear SVM | 70% training (with 5F CV)/30% testing | SVM produced 95.2% 5F CV and 94.2% test accuracy for knee joint detection; 57.6% accuracy in the multi-class KOA severity task (Grades 0-4) |
| Bayramoglu, N          | 2019 | X-ray                 | BoneFinder             | Local Binary Patterns (LBP), Fractal Dimension (FD), Haralick features, Shannon entropy, and Histogram of Oriented Gradients (HOG) | Logistic regression | SVM on OAI for training and validation in MOST data | AUC of 0.84 |
| Chen, P.               | 2019 | X-ray                 | Customized one-stage YOLOv2 network | CNN models (VGG-19) | training, validation, and testing sets with a ratio of 7:1:2 | 69.7% acc |
| Gorizia, M.            | 2019 | X-ray                 | Trainable attention modules | CNN (VGG-16) | 70% training/30% testing and 10% of the training data was kept for validation | 64.3% acc |
| Gornale, Shivanand S.  | 2017 | X-ray                 | Images are cropped to 512 x 409 pixels and finally rescaled | Histogram of orientated gradients (HOG) | Multiclass SVM | Classification results validated by two experts that were in close agreement | Classification rate of 97.96% for Grade-0, 92.85% for Grade-1, 86.20% for Grade-2, 100% for Grade-3 & Grade-4 |
| Liu, B.                | 2020 | X-ray                 | Region proposal network (RPN) | PLA (Faster R-CNN as original and our adjusted model as FLA) | Classification results validated by two experts that were in close agreement | 82.5% acc |
| Mincuillo, L.          | 2017 | X-ray                 | PCA based combination of statistical shape and texture models | PCA-3 stage Constrained Local Model | Indecisive Forest (IF) | 5F CV |
|                       | 2017 | X-ray                 | Statistical Shape Model (PCA) | Random Forest | 87.61% acc | 88.15% acc |
|                       |      |                       |                        |                     |                  | (continued on next page) |
| Author            | Year | Data                  | Localization of joints | Feature engineering | Learning Algorithm | Validation | Results                                                                 |
|-------------------|------|-----------------------|------------------------|---------------------|--------------------|------------|-------------------------------------------------------------------------|
| Minciullo, L.     | 2016 | X-ray                 | Dividing image into blocks | Texture analysis   | SVM                 | -          | ROC AUC of 0.842 (binary) & 0.479 (5-class problem)                   |
| Navale, D. I.     | 2016 | X-ray                 | Dividing Image into Blocks | Texture analysis   | SVM                 | -          | For affected subject, accuracy is 95%                                  |
| Sharma, S.        | 2018 | X-ray                 | Cropping of images     | Histogram method, GLCM and Canny Edge Detection Technique | CNN (ResNet-34)   | 71%-training, 40%-validation and 23.8%-testing                      |
| Tiulpin, A.       | 2018 | X-ray                 | Cropping of images     | Histogram method, GLCM and Canny Edge Detection Technique | CNN (ResNet-34)   | 67%-training, 17%-validation and 22%-testing                        |
| Tiulpin, A.       | 2019 | X-ray                 | Cropping of images-Any eye | Texture analysis   | Random forest regression | -          | The data was split into training, testing, and validation respectively |
| Wahyuningrum, R. T | 2019 | X-ray                 | Cropping of images     | Shape Space, Graph Convolutional Filters | SVM (Gaussian kernel) | 3F CV | 75%-training, 22%-validation                                           |
| Wahyuningrum, R. T | 2019 | X-ray                 | Cropping of images     | Feature engineering | Random forest regression | -          | Up to 94.20%-class accuracy for Grade 1-4                              |

This survey was based on research articles published between 2006 and 2020 using the search engines Scopus, PubMed and Google Scholar. During our search, we identified articles that used ML for the study of KOA by various techniques. Especially, for this search, the terms machine learning, deep learning and knee osteoarthritis were used. A prerequisite for the inclusion of an article in our research was the occurrence of one of the three terms mentioned as keywords, either in the title or in the abstract of each article.

2. Methods

2.1. Literature search approach

This survey was based on research articles published between 2006 and 2020 using the search engines Scopus, PubMed and Google Scholar. During our search, we identified articles that used ML for the study of KOA by various techniques. Especially, for this search, the terms machine learning, deep learning and knee osteoarthritis were used. A prerequisite for the inclusion of an article in our research was the occurrence of one of the three terms mentioned as keywords, either in the title or in the abstract of each article.

2.2. Exclusion criteria

In the first instance, all articles retrieved and collected were examined for the title and the abstract by one of the authors. In order to reach our original goal, we excluded the following categories: non-English articles, postgraduate dissertations, doctoral dissertations, studies not involving people with knee osteoarthritis and studies using traditional technical statistics. All the selected articles have been presented either in journal papers or conferences. Finally, the rest of the authors reviewed again the titles and abstracts to ensure that they met the membership criteria.

2.3. Assessed outcomes

The studies, which are recorded in this article, were divided into four categories, namely (i) Predictions/Regression (13 studies), (ii) Classification (43 studies), (iii) Optimum post-treatment planning techniques (4 studies) and (iv) Segmentation (15 studies). The grouping was based on the technical characteristics of the ML methods and the application domain of each study.

Then, after separating the articles, the following information was extracted from each article: Author, Year of publication, Data (MRI, X-ray, Kinetic and Kinematic data, Clinical data and Demographics), Feature Engineering approach, Learning Algorithm techniques, Validation and Results (evaluation of performance).

3. Results

3.1. Predictions/regression

Despite the fact that OA field has been relatively slow adopting advanced analytical models compared to other fields, nowadays many studies focus on developing ML prediction models for KOA based on medical imaging (Magnetic Resonance Imaging (MRI), X-ray, clinical information, self-reported and biomechanical data.

3.1.1. Data sources

Imaging technologies (either MRI or X-ray) were incorporated into the majority of advanced analytical models to predict knee articular cartilage morphology with accuracies varying from 76.1% up to 92% ([65–69]). Recently, the combination of multimodal data (medical images with clinical or biomechanical data) has formed the basis for more powerful and efficient models. To enhance the quality of the available raw data or overcome the curse of dimensionality, a number of sophisticated algorithms were reported in the literature including: (i) LASSO regression, Topological Data Analysis [71], Recursive feature elimination (RFE) [72], PCA [73] for dimensionality reduction or (ii) CNN [74] to extract new more informative deep features for images. The major finding of these studies was that the accuracy of image-based prediction coding. Recurrent neural networks (RNN) is another important family of DL models that define unique topological connections between their neurons in order to encode temporal information in sequential data [64].
of KOA progression can be improved if it is complemented with data sources such as clinical data, self-reported and biomechanical data.

3.1.2. Learning techniques

Due to their efficiency and predictable performance, ensemble algorithms (RF or Gradient Boosting) were selected in five out of the twelve (12) studies in this category. However, a significant number of studies employed simpler models (e.g. linear regression models [65,75] or logistic regression [71]) to implement the regression or prediction task. Non-linear SVMs were also investigated in four (4) papers ([67,69,72,76]) and this choice could be attributed to the fact that they are relatively efficient in low and medium size feature spaces and that they generalize well. More complex learning (and subsequently more difficult to handle) approaches were finally tested in some studies ([67,69,70]) using NN-based architectures such as Artificial neural networks (ANNs) and CNNs.

3.1.3. Validation

In the majority of those studies, validation has been performed with n-fold cross validation. Hold-out (typically 70%/30% for training/testing) and Leave-one-out cross-validation (LOOCV) have also been observed as a validation approach in some of the studies. It is worth noting that Tiulpin et al. [74] used an independent test set (acquired in another center) for validation. An overview with all the studies including prediction models of KOA are shown in Table 2:

### Table 2

| Author               | Year | Data Feature engineering | Learning Algorithm | Validation | Results |
|----------------------|------|--------------------------|-------------------|------------|---------|
| Chen, H.P. [123]     | 2016 | Biomechanical data Tilt angle calculation and initial posture classification algorithm | Multi-layer SVM | 10-fold cross validation | 90.6% on layer-1 SVM & 92.7% on layer-2 SVM |
| Huang, P.C. [124]    | 2017 | Biomechanical data Sequential forward feature selection (SFS) | Multi-class SVM | 10-fold cross validation | Accuracy for rehabilitation |
| Levinger, P. [121]   | 2009 | Biomechanical data SVM | SVM | LOOCV | Accuracy of 100% for the training set and 88.89% for the test set |
| Wittevrongel, B [122] | 2015 | Biomechanical data k-equal frequency binning | Decision tree & Rule sets | LOOCV | Best accuracy 92.9% & 76.5% respectively |

### Table 3

| Author               | Year | Data Feature engineering | Learning Algorithm | Validation | Results |
|----------------------|------|--------------------------|-------------------|------------|---------|
| Chen, H.P. [123]     | 2016 | Biomechanical data Tilt angle calculation and initial posture classification algorithm | Decision tree & Rule sets | LOOCV | 100% for rehabilitation exercises recognition is 97.7% |
| Huang, P.C. [124]    | 2017 | Biomechanical data Sequential forward feature selection (SFS) | SVM | LOOCV | 97.7% for the test set |
| Levinger, P. [121]   | 2009 | Biomechanical data SVM | SVM | LOOCV | Best accuracy 92.9% & 76.5% respectively |
| Wittevrongel, B [122] | 2015 | Biomechanical data k-equal frequency binning | Decision tree & Rule sets | LOOCV | 100% for rehabilitation exercises recognition is 97.7% |

3.2. Classification

This section presents the outcomes of our survey on the application of classification models on the field of KOA research. It is worthwhile to note the plurality of different datasets along with the heterogeneity of data types used by each study. The identified data sources are: biomechanical data (kinematic-kinetic data and EMG signals), osteoarthritic outcome score, demographic characteristics, some gene polymorphisms, radiographs, X-ray and MRI. For this reason, we are grouping the studies into two categories, the first for biomechanical data-scores and the second for images.

3.2.1. Biomechanical data and discrete variables

3.2.1.1. Data sources. Biomechanical data were the most widely used source of information in the reported studies including kinematic-kinetic data and electromyography signals. Furthermore, clinical data consisting of self-reported, osteoarthritic outcome scores, demographic characteristics and some gene polymorphisms were used as additional sources complementing the biomechanical features.

3.2.1.2. Feature engineering. Feature extraction and dimensionality reduction have been applied to improve the predictive capabilities of the learning models as well as to increase their computational efficiency. A variety of algorithms and techniques were reported in the literature including: (i) Simulated annealing (SA) [78], Genetic algorithms (GAs) [78], Discrete wavelet transform (DWT) ([79,80]), Wavelet Packet [81], SVM-based Fuzzy criteria [81] and Mahalanobis Distance algorithm [82] for feature selection and/or extraction (ii) Probabilistic PCA (PPCA) [83] and PCA ([84–87]) for dimensionality reduction and (iii) feature subsets exploration or use of time-domain statistical features ([88,89]) to lead in more powerful learning models. PCA has been observed to be the most popular feature engineering technique due to its simplicity and easiness to handle.

3.2.1.3. Learning techniques. A variety of machine learning models were used for implementing the detection and/or classification tasks. KNNs and SVMs were the most frequently selected algorithms being tested in (7) out of nineteen studies in this subcategory. Furthermore, RF [90], DT [82], Dempster Shafer Theory [78,85], Bayes classifier [83] and Discriminant analysis [84]) were also investigated. Finally, the use of deep learning techniques (e.g. ANNs [85,91], PNNs [92], MLPs [82,89,93] or CNNs [86,89]) was limited due to the nature of the available training datasets (heterogeneous features and small sample sizes).

An overview of the aforementioned studies is shown in Table 3:

3.2.2. Medical images

Medical images form a crucial source of information in the KOA research. The types of medical imaging that have been analysed in this survey were either MRI or X-ray. According to our knowledge only six studies have been presented in the literature, until now, that reported the development of MRI data analysis methodologies for the diagnosis of KOA. Only one of the aforementioned studies adopted a deep learning approach applying directly learning algorithms (CNN and specifically MRNet) on the available images without the inclusion of any feature selection technique [97]. The rest of the reported studies employed a number of feature engineering techniques prior to the application of the learning models. Discrete wavelet transform, Gray level Co-occurrence Matrix (GLCM) and PCA are among the algorithms that were used to either extract new features or reduce the feature space dimensionality. As regards the learning part, NNs ([98,99]), SVM [100,101] and LDA [102] were the most commonly employed models for early detection and diagnosis of KOA.

Localization of joints was a crucial task in the reported X-ray applications. Numerous approaches of varying complexity were applied such as filtering (Gabor, Sobel) ([103–105]), statistical shape/texture analysis ([106,107]), fully automated software tools (Bonefinder ([108,109])) or more sophisticated deep learning networks including YOLO and FCN ([110,111]). In some cases, manual cropping was also performed ([112–116]). PCA and GLCM were again selected in many of the reported papers to generate small and informative feature subsets, whereas several recent studies adopted CNN-based methodologies as an alternative for the feature extraction task. Deep learning networks (e.g. VGG-19, VGG-16, DenseNet, ResNet-34 and LSTM) were also involved in several studies acting as the main learning algorithm. State-of-the-Art ML models such as SVMs were finally selected in a few X-ray-based studies to drive the decision making process. In most of the cases, validation was performed via k-fold CV and hold-out whereas some studies adopted more robust validation strategies (cross-center validation). The main characteristics of the reported image-based classification studies are shown in Table 4.
### Table 6
Segmentation techniques applied on the KOA research.

| Author                      | Year | Data    | Feature engineering                                                                 | Learning Algorithm                           | Validation                                                                 | Results                                                                 |
|-----------------------------|------|---------|-------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Ababneh, S. Y. [136]        | 2010 | MRI     | Disjoint (non-overlapping) block-wise scanning, two-pass block discovery              | A graph-cut based segmentation algorithm      | 30 images from the OAI database                                           | 96% acc                                                                |
| Ambellan, F. [126]          | 2019 | MRI     | –                                                                                   | Combination of Statistical Shape models (SSMs) and 2D/3D CNN | Datasets: (i) SKII0, (ii) OAI Imorphics and (iii) OAI ZIB                   | (i) 7.40 ± 7.7 Total score                                              |
|                            |      |         |                                                                                     |                                               | (ii) For femoral cartilage the DSC is 89.4%; for baseline and 89.1%       | (ii) For femoral cartilage the DSC is 89.4%; for baseline and 89.1%       |
|                            |      |         |                                                                                     |                                               | (iii) The DSC is 98.6% for femoral bone, 98.5% for tibial bone, 89.9% for femoral cartilage, and 85.6% for tibial cartilage | (iii) The DSC is 98.6% for femoral bone, 98.5% for tibial bone, 89.9% for femoral cartilage, and 85.6% for tibial cartilage |
| Gan, H. S. [125]            | 2017 | MRI     | k-means clustering algorithm, Fuzzy c-mean                                          | Flexible seeds labelling method               | Manual validation by two experts on 10 images                              | Dice’s reproducibility of 0.80 for observer 1 and 0.83 for observer 2 |
| Gornale, Shivanand S. [152] | 2019 | X-Ray   | ROI extraction using Sobel, Prewitt edge detection, Computation of basic statistical features | Otsu’s Segmentation, Texture based Segmentation and KNN | 532 digital Knee X-ray images                                               | The accuracy rate of 91.16% for Sobel method, 96.80% for Otsu’s method, 94.92% for texture method and 97.55% for Prewitt method is obtained |
| Kashyap, S. [134]           | 2016 | MRI     | Extraction of 3D Haar-like features from volume of interest (VOI)                  | LOGISMOS, just-enough interaction (JEI) as post-processing and Random Forest Classifier | The data from OAI were divided into two training sets with 15 and 13 which were used to train the NAF and the second RF classifier. 53 data-sets were used for testing | Border positioning errors (mm)                                          |
|                            |      |         |                                                                                     |                                               |                                                                            | Femur signed 0.03 ± 0.19                                                |
|                            |      |         |                                                                                     |                                               |                                                                            | Tibia signed 0.10 ± 0.17                                                |
|                            |      |         |                                                                                     |                                               |                                                                            | Tibia unsigned 0.61 ± 0.14                                              |
|                            |      |         |                                                                                     |                                               |                                                                            | For RF classifier:                                                       |
|                            |      |         |                                                                                     |                                               |                                                                            | Femur signed – 0.06 ± 0.18                                              |
|                            |      |         |                                                                                     |                                               |                                                                            | Tibia signed 0.56 ± 0.11                                                |
|                            |      |         |                                                                                     |                                               |                                                                            | Tibia signed 0.16 ± 0.24                                                 |
|                            |      |         |                                                                                     |                                               |                                                                            | Tibia unsigned 0.65 ± 0.17                                              |
| Kashyap, S. [135]           | 2018 | MRI     | Neighborhood Approximation Forests k-means clustering                               | Hierarchical Random Forest Classifier and LOGISMOS | 108 MRIs from baseline, and 12 month follow-up scans of 54 patients       | Cartilage surface positioning errors (in mm) of 40                        |
| Mantal, K. [133]            | 2011 | MRI     | Histogram equalization, extraction of similarity features from neighboring patches and PCA | K-means                                       | MRI scan from 50 subjects (25 for training)                                | Femur signed 0.01 ± 0.18                                                |
|                            |      |         |                                                                                     |                                               |                                                                            | Femur unsigned 0.53 ± 0.11 at Baseline                                  |
|                            |      |         |                                                                                     |                                               |                                                                            | Average sensitivity, specificity and dice similarity coefficient of 0.853 ± 0.093, 0.999 ± 0.001, 0.800 ± 0.106 and 0.831 ± 0.095, 0.999 ± 0.001, 0.777 ± 0.054 on tibial and femoral cartilages respectively |                           |
| Panfilov, E. [129]          | 2019 | MRI     | –                                                                                   | Deep learning U-net with two modern regularization techniques, namely, supervised mixup and UDA | 5-fold cross-validation, Dataset A: 88 MRI images, Dataset B: 108 MRI images and Dataset C: 44 MRI images | Mean of volumetric DSCs is 0.907 (U-net + mixup, Dataset A) for femoral cartilage and DSCs is 0.821 (U-net + UDA2, Dataset C). |
| Park, S-H. [137]            | 2009 | MRI     | Combined Intensity and Shape Priors                                                | Iterative Local Branch-and-mincut             | LOOV on 8 3D MRI images                                                   | Average similarity index over 0.80 for normal participants and 0.75, 0.67, and 0.64 for participants with established knee OA |
| Swanson, M. S. [138]        | 2010 | MRI     | Manual selection of seed points, histogram and fitted Gaussian curves of the region | Threshold operation followed by conditional dilation and post-processing | Validation on 10 normal knees images and 14 knees with OA                  | Mean similarity Index 0.64–0.80                                         |
| Tack, A. [127]              | 2018 | MRI     | 2D U-net followed by statistical shape models of menisci                            | CNN (3D U-Net)                                | Validation on 5 different datasets of MRI images from OAI with 2F CV      | DSCs was 83.8% for medial menisc (MM) and 88.9% for lateral menisc (LM) at baseline, and 83.1% and 88.3% at 12-month follow-up. |
| Tack, A. [128]              | 2019 | MRI     | –                                                                                   | 3D CNN (3D U-Nets)                            | MRI data of 1378 subjects from the OAI (2F CV)                           | Accuracy of 88.02 ± 4.62 for medial tibial cartilage (MTC) and 91.27 ± 2.33 for lateral tibial cartilage (LTC) at baseline and 87.43 ± 4.02 and 90.78 ± 2.42 at 12-months follow-up |                           |
| Tamez-Pena, J. G [139].     | 2012 | MRI     | Manual creation of atlases by experts using CIPAS Anatomically-based joint area proposal and Histogram of Oriented Gradients | Multi-atlas segmentation using CIPAS platform SVM | LOO on 48 MRI images                                                      | DSC 0.88 and 0.84 for the femoral and tibial cartilage                   |
| Tiulpin, A. [131]           | 2017 | X-ray   | –                                                                                   | Hourglass-like encoder-decoder models for landmark localization | The images from MOST were used to create training (991), validation (110) and test sets (473), Jyvaskyla (93), OKOA (77) | Mean intersection over the union equals to: 0.84 (MOST), 0.79 (Jyvaskyla) and 0.78 (OKOA). |
| Tiulpin, A. [130]           | 2019 | X-ray   | ROI localization using low-costs annotations                                       | Hourglass-like encoder-decoder models for landmark localization | 5-fold patient-wise cross-validation split stratified by a KL grade (748 knee joints in total) | Precision 92.11 ± 0.34 at 2.5 mm                                        |
3.3. Optimum post-treatment planning techniques

As concluded in this survey, there is a lack of studies on the development of ML-based decision support systems (DSS) for the post-treatment stage of KOA. According to our knowledge, the first attempt in that direction was made in 2009 in Ref. [121] where the authors presented an approach for detecting recovery from knee replacement surgery using gait spatio-temporal parameters. Their main aim was to investigate if the classifier could detect changes at 2 and 12 months following knee replacement surgery. The proposed method achieved to: (i) detect improvements in gait function and (ii) recognize gait parameters that are altered due to KOA. In Ref. [122], the authors tackled the task of selecting the appropriate gait re-training strategy as a ML problem and presented interpretable learning models. Using the trained models, a specialist was able to know which technique would work best for a specific patient. Online segmentation for KOA rehabilitation monitoring was also investigated in Ref. [123]. The novelty of this system was the real-time feedback to patients and physiotherapists. Finally, a SVM-based human motion identification for rehabilitation exercise assessment of KOA was proposed in Ref. [124] using biomechanical data with reliable results (up to 100% in recognizing the types of rehabilitation exercises and over 97.7% in motion identification). In the majority of the reported studies, the SVM technique was applied (in three out of four reports) on biomechanical data leading to even perfect identification rates (up to 100%). The validation was performed with 10-fold cross validation or with the leave one out (LOO) cross-validation approach. The studies with the ML-empowered post-treatment planning techniques of KOA are shown in Table 5.

![Temporal evolution chart](image1)

![Bubble chart](image2)
3.4. Segmentation

Image segmentation is the process of changing the representation of an image into meaningful segments. MR image segmentation for KOA is typically performed by clinicians following a manual, laborious, time-consuming process that is prone to subjective diagnosis error. Therefore, many studies have focused on interactive, semi or fully automated cartilage segmentation to assist the medical research in KOA. At this point, it should be mentioned that even in the case of ML and especially in supervised learning approaches, a researcher/doctor still needs to label the images, hence the developed trained model is prone to the subjectivity.

3.4.1. Landmark localization and shape modelling

To increase the performance of medical image segmentation techniques, landmark localization and shape modelling have been utilized as preliminary tools before the application of ML or DL. As recorded, landmark localization took place by using either hourglass-like encoder-decoder models or with manual cropping and selection of seed points. Furthermore, a number of shape modelling tools were employed to extract informative shape-relevant characteristics from the available images including: Statistical Shape Models (SSMs), Combined Intensity, Shape Priors, Histogram of Oriented Gradients (HoG) and edge detectors.

3.4.2. Segmentation

Segmentation was accomplished employing either interactive or (semi- and/or fully) automated approaches. Flexible seeds labelling applied on MRI data [125] was the dominant approach on the integrative segmentation category. To enable automation on the segmentation tasks, advanced DL-based techniques were adopted (e.g. CNN ([126–128]), unsupervised domain adaptation DL [129] and DNN [130]) or even state-of-the-art ML techniques such as SVM ([131]), KNN ([132,133]) and RF ([134,135]). Finally, more traditional segmentation approaches were also proposed including: two-pass block discovery mechanism [136], Iterative Local Branch-and-mincut [137], Gaussian fit model [138] and multi-atlas segmentation (MAS) [139].

3.4.3. Validation

OAI and MOST were the most-used databases to validate the performance of the aforementioned segmentation approaches. Validation was performed using k-Fold CV, LOOV or even manual assessment from experts. An overview of all the identified KOA segmentation studies of our survey is given in Table 6:

4. Discussion and conclusions

Our literature survey outlined the current usage of machine learning methods in KOA diagnosis and prediction challenge. Fig. 2 shows an increasing trend of ML-related studies and papers in the field of KOA indicating the need for (i) enhancing our understanding about the onset and progression of the disease and (ii) new data-driven tools that could enable early diagnosis and prediction of KOA. ML could play a key role towards these directions extracting valuable knowledge from various types of clinical data (biomechanical parameters, images, kinematics) and finding new solutions that utilize data from the greatest possible variety of sources.

Data has to be seen as an asset being one of the most important and instructive assets of the healthcare industry. In KOA research, several data sources have been considered as inputs forming powerful multi-dimensional training and testing data sets. Medical Imaging is one of the dominant data sources of the sector with MRI and X-ray images being typically employed in the majority of the papers of our survey (25 and 25 papers out of 75 used MRI and X-ray, respectively). Biomechanical parameters were also investigated in 21 studies demonstrating a big potential to be useful input data in KOA diagnosis, prognosis and the post-treatment planning. Finally, other complementary data sources have been also considered in KOA research in several papers including pain, outcome scores, demographics, generic attributes and genes (Fig. 2).

Feature engineering algorithms were applied on the available clinical data to either reduce the input feature dimensionality or extract new informative parameters from the raw data. PCA was employed in a number of papers to compress 3D kinematic time-series, ground reaction forces and MRI/X-ray images into more compact representations. Time domain and time-frequency domain features (e.g. DWT or Wavelet packet) were also extracted from GRF or EMG signals. GLCM was proved to be a quite popular technique for extracting textural features in studies where MRI or X-ray images are considered as inputs. A number of feature selection techniques has been also employed to select the most informative features from the pool of the available or extracted parameters. Partial least squares, simulated annealing, random selection and sequential forward FS were among the techniques that were used to reduce the feature dimensionality of the initial space so as to increase the computational efficiency as well as generalisation capability of the subsequent classification or regressing models. Pre-trained CNN models were finally employed to extract valuable information for clinical images.

As far as the type of the ML models that were reported in our survey, SVMs were proved to be the most frequently used model in all the survey categories. Four (4) SVM-based studies were identified in the knee OA prediction survey, whereas another ten (10) papers made use of SVM for classification purposes including biomechanical discrete parameters or images (mostly MRI and X-ray). Moreover, SVM was also employed in three (3) out of the four (4) papers in the post-treatment survey. The choice of SVM could be attributed to the fact that they generalize well in practice and that are computationally effective in high dimensional spaces. Neural networks were the second most frequent technique with three (3) studies reported for knee OA prediction and eighteen (18) applications of NN-based models in the OA classification survey. Convolutional neural networks were finally considered in studies where clinical images were used as inputs. CNN-based approaches were either employed for feature extraction and/or for quantifying the severity of knee OA.

Nowadays biomedical research and clinical practices on KOA are struggling to cope with the growing complexity of interactions with the gained knowledge being fragmented and associated either with molecular/cellular processes or with tissue and organ phenotype changes related to clinical symptoms. Therefore, KOA is a big data problem in terms of the big data complexity and not the data size as it has been commonly considered in the literature. To tackle this huge complexity challenge, a multidisciplinary research approach should be proposed in the future across many disciplines: biomedical modelling via mechanistic analyses at various scales to capture locally the available knowledge into predictive simulations; medical imaging and sensing technologies to produce quantitative data about the patient’s anatomy and physiology; data processing to extract from such data information that in some cases is not immediately available; big data analytics and computational intelligence tools that will generate personalised ‘hyper-models’ under the operational conditions imposed by clinical usage. Machine learning can explore massive design spaces to identify correlations and multiscale modelling can predict system dynamics to identify causality. This has the potential to lead to the development of individually tailored treatments to maximize the efficacy of treatment. Research work at the intersection of machine learning and KOA offers great promise for improving clinical decision-making, and accelerating relevant intervention programs. To enable appropriate adoption of advanced learning algorithms and stay tuned with the new developments in ML/DL that are embracing research to other medical fields, open data, tools, and discussions must be forceful encouraged within the KOA research community.

Declaration of Competing Interest

None.
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