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Review

Comparative analysis of breast cancer detection using machine learning and biosensors

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ABSTRACT

Breast cancer is a widely occurring cancer in women worldwide and is related to high mortality. The objective of this review was to present several approaches to investigate the application of multiple algorithms based on machine learning (ML) approach and biosensors for early breast cancer detection. Automation is needed because biosensors and ML are needed to identify cancers based on microscopic images. ML aims to facilitate self-learning in computers. Rather than relying on explicit pre-programmed rules and models, it is based on identifying patterns in observed data and building models to predict outcomes. We have compared and analysed various types of algorithms such as fuzzy extreme learning machine – radial basis function (ELM-RBF), support vector machine (SVM), support vector regression (SVR), relevance vector machine (RVM), naive bayes, k-nearest neighbours algorithm (K-NN), decision tree (DT), artificial neural network (ANN), back-propagation neural network (BPNN), and random forest across different databases including images digitized from fine needle aspirations of breast masses, scanned film mammography, breast infrared images, MR images, data collected by using blood analyses, and histopathology image samples. The results were compared on performance metric elements like accuracy, precision, and recall. Further, we used biosensors to determine the presence of a specific biological analyte by transforming the cellular constituents of proteins, DNA, or RNA into electrical signals that can be detected and analysed. Here, we have compared the detection of different types of analytes such as HER2, miRNA 21, miRNA 155, MCF-7 cells, DNA, BRCA1, BRCA2, human tears, and saliva by using different types of biosensors including FET, electrochemical, and sandwich electrochemical, among others. Several biosensors use a different type of specification which is also discussed. The result of which is analysed on the basis of detection limit, linear ranges, and response time. Different studies and related articles were reviewed and analysed systematically, and those published from 2010 to 2021 were considered. Biosensors and ML both have the potential to detect breast cancer quickly and effectively.

1. Introduction

Technologies in healthcare include maintenance and retrieval of electronic medical records of patients and devices involved. Cancer detection has always been a challenge in the diagnosis and treatment plan for haematological diseases. Currently, an overwhelming percentage of the population is affected by one or more diseases. Recent years have seen tremendous advances in medical science. Despite these advancements, there is still a huge lack of information among the public regarding health and disease. A large proportion of the population likely suffer from health issues, some of which may even be fatal [1]. In addition to improving the accuracy of the rapid detection of fatal conditions, adopting safe, realistic techniques and using modern technology can reduce the need for caregivers and reduce overall health care costs. Several lives could be saved through innovations in intelligent decision-making strategies [2] and technologies [3–4].

Cancer is characterized by the rampant and aberrant growth of cells due to a combination of characteristic genetic and epigenetic defects. This uncontrolled growth of the cells contributes to tumour development. If the tumour begins to rapidly metastasize to other organs and systems of the body as the cancer progresses, the disease may already be incurable when discovered [5]. Breast cancer primarily affects women (with < 1% of cases affecting non-females); roughly one in eight women develop breast cancer in their lifetime [6]. Roughly 2.1 million women are diagnosed with breast cancer annually, and the most severely affected are those between the ages of 40 and 70 years [7]. Therefore, the early diagnosis of breast cancer is paramount to good prognosis. Despite the fact that the symptoms may be weak in the early stages, chances of

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survival dramatically increase if detected early [1]. The various screening methods used to diagnose breast cancer include fine needle aspiration cytology (FNAC), ultrasound-guided surgical biopsy, and mammography. In dense breasts, the rate of cancer detection using mammography is very poor and about 10%–30% of cases go undetected [8–9]. It is important to identify cancer cells accurately to decrease mortality rates, and this involves effective early cancer diagnosis and treatment to increase the survival rate of cancer patients [10–13].

Machine learning (ML) is one of the most popular models to easily train machines and create predictive models for successful decision-making. Machine learning helps with early diagnosis of breast cancer and determines the nature of the cancer by analysing the tumour size. Machine learning methods are the leading approaches to obtain favourable outcomes among classification and prediction problems. Breast cancer research could benefit from ML techniques used to identify cancer and predict the presence or absence of tumours. Machine learning techniques can also be used to predict tumour malignancy [14–15]. To diagnose and monitor the diseases, conventional methods used are highly based on the detection of the presence of specific signal features by a human observer. In the past decade, the development of several computer-aided diagnosis (CAD) approaches have been prompted by many patients in intensive care units requiring constant monitoring. The predominantly qualitative diagnosis criteria are turned into a more concrete quantitative feature to improve upon the issue of classification in these techniques [16–17]. Multiple classifiers were tested on three separate datasets, from the point of view of classification accuracy. Classifiers like sequential minimal optimization and multilayer perceptron (MLP) were also included in the study apart from classifiers such as Naive Bayesian, IBK, and Decision Trees. The above were tested on various datasets which mainly consisted of the Wisconsin Breast Cancer (Original) Dataset (WBCD) and other Wisconsin Datasets such as the Breast Cancer Wisconsin (Diagnostic) Dataset(WDBC) and Breast Cancer Wisconsin (Prognostic) Dataset(WPBC). For the WDBC dataset, the MLP and J48 classifiers were fused and assisted by the feature selection method that exhibited a higher accuracy rate than non-fused versions. For the WPBC dataset, the fusion of all four above-mentioned ML algorithms exhibited a greater accuracy in finding tumour than conventional methods, while the suggested SMO proved to be a better approach and more precise for the WDBC dataset. Further, Salama et al. suggested a multi-classifier by figuring out which one of the fused classifiers would provide the best performance for any particular dataset [18–19]. The Breast Cancer Model with ML algorithms is represented in Figure 1. The model can be used for the prediction of benign and malignant cancer cells. First, the Breast Image data is loaded, then Feature Extraction takes place, and then the final classification model can be trained to fulfil the task stated above. Malignant cancer begins with irregular cell growth and can quickly spread to or infiltrate the surrounding tissues, which makes it a life-threatening condition; by contrast, benign tumours are considered non-cancerous and usually, non-lethal [15,20].

The International Union of Pure and Applied Chemistry (IUPAC), the world authority on chemical nomenclature and terminology, did not provide a formal definition for biosensors until 1997. A biosensor works in a way that can detect abnormalities in the human body by monitoring biomarkers within the human body. Mammogram screening is recommended for women at normal risk of breast cancer and, by combining this with certain biomarkers, we can increase the chances of early detection. The main objective for the designing of a biosensor was to detect bio-analytical molecules from various samples. It was integrated in a way to fuse three different areas of science-chemistry, biology, and engineering-into a single device [21-22]. The presence of a tumour biomarker could indicate cancer in the human body [23]. Biomarkers for breast cancer can be categorised into one of the three types: prognostic, diagnostic, and therapeutic; based on the severity of the cancer, their presence can be detected [24-25]. Clinical and medical teams have recognized several tumour biomarkers for determining the presence of cancer in an individual, and several specific

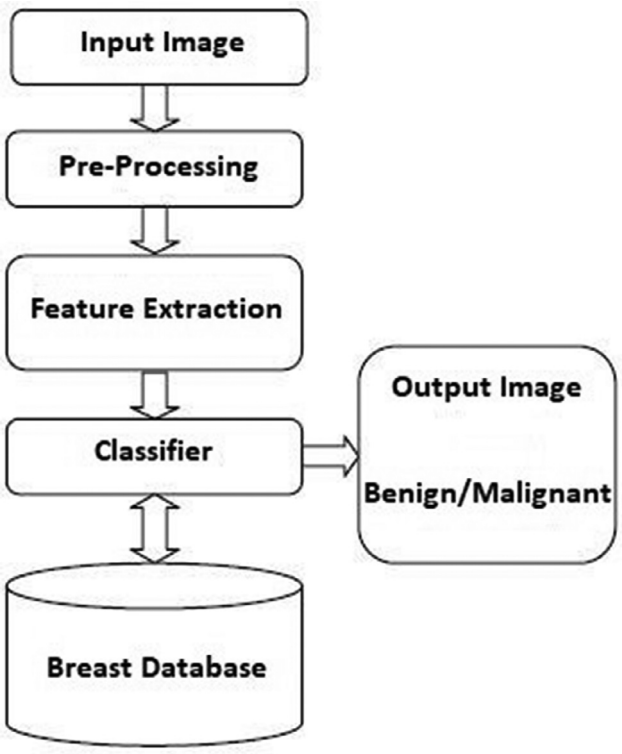

Figure 1. Block diagram of the breast cancer recognition system.

fluid-based biomarkers are taken into account for the production of electrochemical biosensors. Gene- or immune-based sensors are some examples of modern electrochemical bio-affinity sensors that provide exceptional sensitivity, which is an essential tool for the detection of early-stage cancer. Electrochemical devices are highly efficient, and offer clinical advantages in identifying cancer and monitoring treatment as well as a more precise method of detection. Advancement of these portable devices will be crucial to quicken the process of cancer diagnosis and rapidly obtain analytical results [26]. Electrochemical biosensors are among the best options for biochemical analysis given their added advantages of ultra-sensitivity, cost efficiency, simplicity of preparation and background as well as several unlisted advantages [13, 27–30].

2. Search methodology and article selection

In this literature review, relevant articles were retrieved by querying terms like [“Breast Cancer” or “Cancer Detection”] + “Machine Learning” + [“SVM or ANN”] + [Biosensors or FET or Electrochemical”] in the following databases: Google Scholar, Research Gate, PubMed, Science Direct, IEEE, and Springer.

All the applications where breast cancer detection can be used have been discussed in this review. Studies conducted prior to 2010 are considered to be less relevant as the techniques introduced had less accuracy, were costly, and the scope of implementation was comparatively less.

3. Advanced technology in breast cancer detection

Technological advancement in the medical sector has continuously increased over the years. There are various technologies deployed for breast cancer detection. The major ones among these are presented in Figure 2.

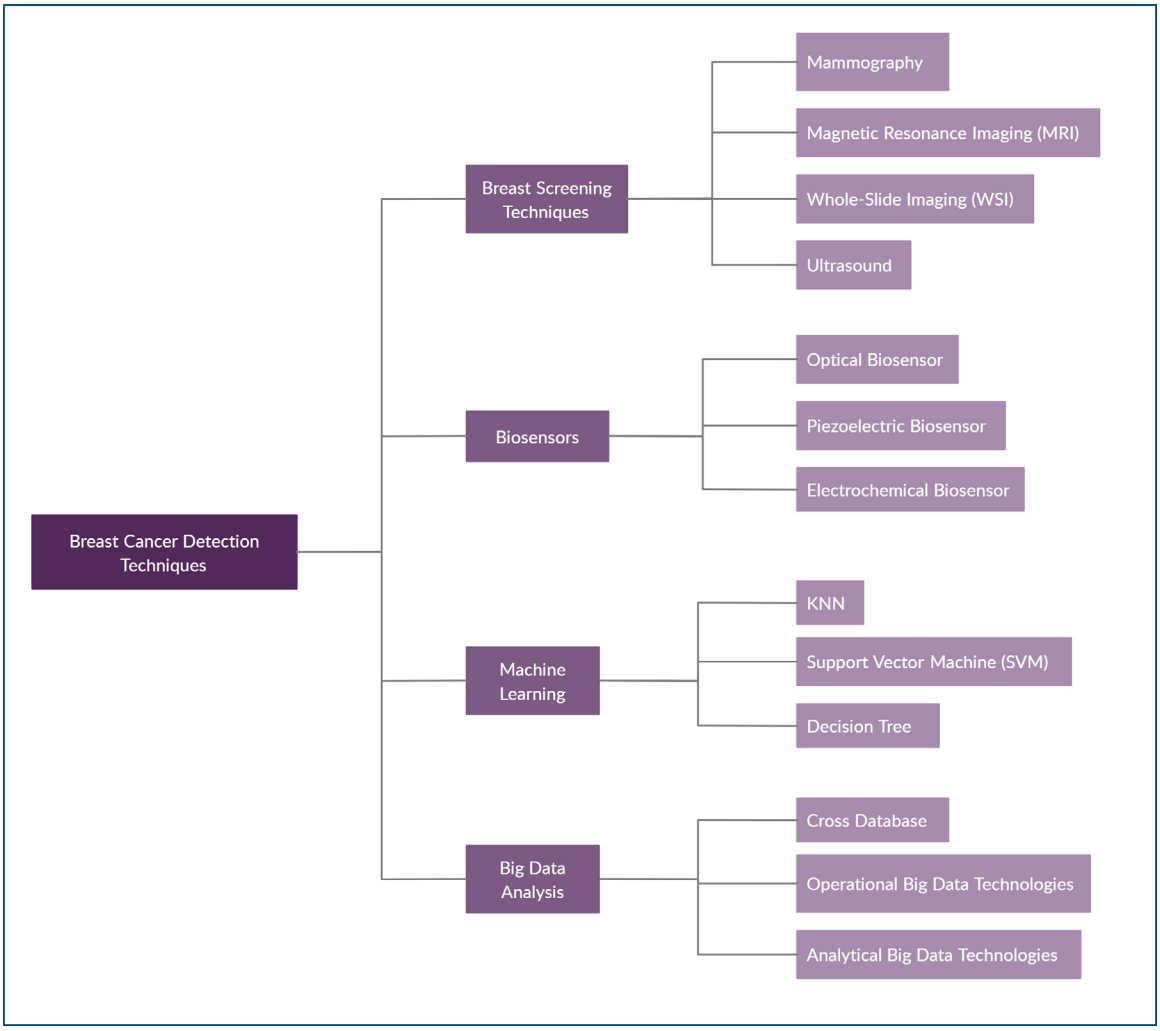

Figure 2. Technologies used for breast cancer detection.

3.1. Breast screening techniques

Breast Screening refers to the early detection of diseases by testing before symptoms appear. Genetic tests to identify inherited diseases and physical or imaging-related examinations are all examples of testing that can be done as part of a screening test. Breast cancer screening involves modalities such as mammography, magnetic resonance imaging (MRI), whole-slide imaging (WSI), and ultrasound.

3.2. Biosensors

Biosensors are analytical devices used to quantify the biological characteristics of tissues and body fluids [31-32]. Some examples of biosensors include optical biosensors, piezoelectric biosensors, and electrochemical biosensors.

3.3. Machine learning

ML techniques are widely recognized as the method of choice in breast cancer pattern classification and decision forecast modeling as it provides certain unique advantages in the critical feature detection from the overall complex datasets. KNN, SVM, DT methods have shown promising results in the classification of data. Moreover, these methods greatly help in clinical decision-making and diagnosis.

3.4. Big data analysis

Big data methods allow experts to exploit data sources, including unstructured ones such as textual patient reports or images; thereby influencing medical research and ultimately patient care [33]. Cross-Database, Operational Big Data, and Analytical Big Data are some of the methods used in Big Data analysis.

Usually hailed as the gold standard for breast imaging and diagnosis, screen-film mammography is widely used for breast imaging [34]. Mammography is used as a breast cancer detection, diagnostic, and screening tool and involves examining the human breast using low-level X-rays [35-36]. Mammography is considered a good method for the detection of ductal carcinoma *in situ* (DCIS) and calcifications. Before lesion manifestation, breast cancer screening is best used for detecting early-stage cancer. Since the advent of mammography, the mortality rates due to breast cancer have seen a dip. Mammography has a sensitivity of 67% for true positives. Although widely accepted through the years, the detection of breast cancer by mammography is presently considered quite weak when compared to other more advanced techniques. Some of the disadvantages of mammography include radiation exposure and a high false-positive rate. It is also possible that the radiologist in charge of the diagnosis might occasionally miss a detail and generate a false-negative report. Last, this method is not very sensitive for detecting early-stage cancer in women with dense breast tissue [37].

With time, biosensors are being widely accepted, as they have demonstrated excellent selectivity in recent times to isolate and distinguish the complementary sequences from the non-complementary ones, showing promising outcomes for breast cancer diagnosis [38]. DNA-based biosensors and electrochemical DNA biosensors are very attractive compared to other various types of biosensors due to their high sensitivity, simplicity, and miniaturization [39-41]. There are many ways in which the biosensors interface with each other on a molecular level; these include methods where the electric signal is obtained from hybridizing with the target DNA and from the DNA probe itself [39, 41]. Given the simplicity of the process and application for nucleic acid hybridizations that have been useful in the detection of several diseases, some of which include tuberculosis [42], meningitis [43], and lung cancer [44], DNA-biosensor-based diagnostics have attracted considerable attention in the field of breast cancer detection too [41]. In contrast to detection of biological cells and imaging of biomolecules, electrochemical nano biosensors have many advantages, including low cost, versatility, high sensitivity and precision, durability, and rapid response. Variables such as capture efficiency, nanomaterials, and the size of the sensors considerably affect the sensitivity of electrochemical nanobiosensors [34]. Even though biosensor and biomarker-based techniques are on the rise, it comes with its own set of limitations. These techniques, although sensitive and selective, are associated with certain problems. Biomarker-based techniques are quite expensive and also require trained personnel for the labelling process. They are also highly time-consuming, which discourages its wide adoption [24, 34].

Medical diagnosis using ML techniques has gained considerable momentum in the past decade. This growth in the adoption of ML techniques is partly due to the fact that it affords better diagnosis of several diseases, attributed to improved symptom detection. Further, ML also helps to design a more personalized therapeutic proposal, as results of the analysis can be used to submit new diagnostic hypotheses [45]. Breast cancer detection methods that have been employed utilizing ML algorithms include SVM, decision trees, and neural networks. The most widely adopted and the most useful ones are neural networks (NNs) and DTs. However, their working mechanisms are quite different. The main benefit of using a decision tree-based ML model is that the algorithm used is easy to understand and has also been proven to be quite efficient. Moreover, the order of the training instances shown does not affect the training efficiency of the model. Many ML models suffer from overfitting; however, pruning in the decision tree addressed this problem of overfitting. Nonetheless, the decision tree-based ML model also has some limitations. They come with the prerequisite that the data classes must be mutually exclusive. The end result decision tree is dependent upon the order in which the attributes were selected. Overly complex and difficult-to-interpret decision trees can be obtained owing to certain errors while training. Furthermore, the missing values of certain attributes can lead to confusion in the decision tree [46]. Neural networks can be used to address the issue of classification or regression. Representation of Boolean functions is also unlocked using neural networks, and they can handle noisy inputs with ease. However, neural networks are more complex and difficult to understand than the simple working of decision tree algorithms. Moreover, the use of too many attributes can lead to overfitting-a problem that does not exist when using decision trees [47].

4. Machine learning in breast cancer detection

ML is a subfield of artificial intelligence (AI) that uses soft-coding instead of the conventional hardcoded approach. ML refers to the mechanism wherein despite an absence of explicitly programmed instructions, the machine can continue to learn from experience [48-49]. In cancer research, ML models have a long history of being helpful with not just the research but also with the practical implementation in cancer detection [46]. For almost 30 years now, decision trees and artificial neural networks have helped in the detection and diagnosis of cancer. Almost 20 years have passed since the introduction of the SVM based models as a prognostic model for cancer [6]. Several optimized systems have been introduced for image processing in the medical sector such as CADe and CADx systems with the help of several algorithms based on ML. CADe systems help detect objects that hold a high significance in clinical terms, while CADx systems help quantify the malignancy of the clinical objects that are detected either manually or automatically [50-51]. Various data mining algorithms and techniques have been applied in the several studies conducted on a multitude of datasets to classify breast cancer. The primary advantage of such techniques and algorithms is their superior classification results. This has led to many researchers incorporating techniques like data mining and the use of optimized ML models into their studies that revolve around solving challenging and convoluted tasks [52].

Researchers have also worked on increasing the accuracy for the survival time prediction for someone diagnosed with breast cancer, by using ML [6]. Essentially, this study attempts to evaluate the efficiency and accuracy of the ML algorithms already in place for predicting survival time. The authors proposed an approach that used ML and added a new feature based on the concatenation of three features, namely tumour stage, tumour size, and age at the time of diagnosis, into a single new feature. Then, they applied ML models using Support Vector Machine - Regression (SVR). The methods used by them provided optimistic results. The authors also showed that more accurate predictions could be made using both linear and decision tree-based regression models of SVR and confirmed the same using cross-validation. Last, they concluded that the new tumour integrated clinical feature (TCIF) outperformed the existing Nottingham prognostic index (NPI) feature.

Asri et al. [53] proposed an interbred classifier based on the approach of knowledge discovery to detect the presence of breast cancer. The paper's objective was to perform a thorough analysis and provide a comparison of the various ML algorithmic programs like SVMs, Naive Bayes, *K*-Nearest Neighbours, and DTs. The WBCDs were used to implement the algorithms. Their main aim was to assess the performance of the algorithms on multiple parameters to develop a novel fusion algorithm that would display optimal execution. Based on their experiments, the authors found that a classifier that fused three model types of SVM, NB, and C4.5 could achieve 97.31% accuracy, which was the best performer. They showed that this novel approach of using multi-classifiers was quite efficient and reliable in the prediction of breast cancer and its diagnosis. They also concluded that building an accurate and computationally efficient classifier is a real challenge given that patients' lives depended on it and should therefore be carefully monitored.

Sadhukhan et al. [54] employed a model, based on the variables from the cell nucleus, that had been trained using ML. The algorithms at work in this study were K-NN and SVM. The performance of their classifiers was determined and analyzed. With the help of a Bayesian Network, they aimed to compare and contrast the task using a dataset containing the feature values that were collected from the images of cell slides using FNAC. Their research showed that all attempts were directed towards developing an algorithm that enables one to predict whether the tumour is malignant or benign. The image provided had varying illumination at various locations that would differ depending on the intensity of illumination. Three levels of classification were applied to the image: black, white, and grey. The model showed a significantly high level of efficiency (97.49%). Therefore, the authors concluded that faster diagnosis of breast cancer could be achieved in the future using a process whereby the slide images from the cells obtained by FNAC could be pre-processed using automation to extract the relevant features and immediately be fed directly into the ML-based model.

Based on the Wisconsin Breast Cancer dataset and by measuring the performance of the 11 ML algorithms used for the classification task, a comparative analysis between them was presented by Benbrahim et al. [7]. To differentiate between benign and malignant breast lumps, the authors proposed a method for developing two classifiers using the features derived from the post-diagnosis images from FNAC. They aimed

to examine and analyze the accuracy of the given 11 different ML algorithms and conclude which one would provide the best result. The results of the experiments showed that the neural network proved to be the most accurate among all the other 11 with an accuracy index of 96.49%, followed by linear discriminant analysis (LDA) and logistic regression (LR), and then random forest (RF), decision tree (DT), and Support Vector Classifier (SVC) (linear). They concluded that in the future, the neural net algorithm could be deployed and implemented into a Big Data test that might perform better over present modules like Hadoop and Apache Spark.

Osmanović et al. [55] collected data from 699 samples at the UCI ML repository. The artificial neural network (ANN) used for this study was configured such that it could make use of nine neurons (number of attributes) and a single output neuron (the nature of the lump i.e., benign or malignant). A backpropagation network-specific confusion matrix was also presented. The results indicated that there was a 99% chance of correct diagnosis if the ANN was functionally deployed. This also indicated that there was a 97.6% chance of them being negatively classified. The ANN still has scope for further improvements in the future. It could help doctors with a faster method of diagnosis and also monitor the patient's condition. The authors proposed to develop a graphical user interface (GUI)-based tool for ease of use by doctors who are not particularly adept in using such tools without a proper interface.

Negi et al. [56] presented four ML model-based algorithms for breast cancer detection: Bayesian networks, kNN, SVM, and random forest. The authors aimed to develop a meticulous approach for diagnosing and classifying breast cancer. In contrast to the random forest method, the Support Vector Machine (SVM) method achieved optimal accuracy and distinctiveness, with the former coming up with the greatest probability of classifying tumours appropriately. With the help of properties such as training time for a small and large dataset, recall, area under the receiver operating characteristic curve, accuracy of the predictions made, and roll-up of the feature count, an accurate comparison can be drawn. Their study showed that there is still scope for future investigation in the field.

Al Bataineh used the WBCD dataset and presented a direct comparison among five algorithms for breast cancer diagnosis: Multilayer Perceptron, kNN, Classification and Regression Trees, NB, and SVM [15]. Throughout the study, the primary objective was to evaluate the performance of the various ML methods by evaluating the reliability, accuracy, and precision of each algorithm individually for data classification. The aim was to discover which ML method could predict the nature of the tumour. Their results showed that the Multilayer Perceptron model offered optimal performance in terms of precision, recall, and accuracy. The accuracy shown by the MLP on the training data was 96.70%, which outperformed other algorithms. These models were later tested on unseen data to analyze their real-world performance.

Asri et al. [57] presented four different classification algorithms with comparison and contrast between them: Support Vector Machine, Naive Bayes, kNN, and C4.5 decision trees. Based on the performance measures of sensitivity, precision, specificity, and accuracy, they sought to evaluate the algorithms' efficiency and effectiveness. The Weka ML environment was used to derive all the classifiers employed by them. The WBCD was used in their study which comprised 699 cases, 458 of which were benign and 241 were malignant, which are spread across two classes and 11 features, with 65.5% of malignant tumours and 34.5% benign tumours. They applied a method known as the *K*-Folds cross-validation. The value of k was selected as 10 to achieve the least amount of bias. The results from the model were later evaluated using *K*-Folds cross-validation. These researchers assessed the performance results in terms of five metrics: the Kappa statistics, the Mean Absolute Error, the Root Mean Squared Error, the Relative Absolute Error, and the Root Relative Squared Error. Based on the results of their experiment, they found that the SVM-based model could achieve the best performance with an accuracy of 97.13% and the lowest rate of error was 0.02%. The performance of the ML model based on other algorithms varied between 95.12% and 95.28%, and the error rate varied between 0.03 and 0.06. They observed a large number of incorrect classifications with the C4.5 algorithm and for the *k*-NN algorithm (34 and 33 incorrect instances, respectively). Lucas Borges reported a comparison of two ML techniques-Bayesian network algorithm and J48. They mainly worked with the WBCD dataset and developed two classifiers to distinguish benign from malignant lesions [58]. The pre-processing of data is an important step before running the algorithm, as it would not be able to deal with missing values otherwise. Moreover, the performance of the model would be enhanced by supervised learning. Further, by decreasing the number of values inside the continuous data using label encoding, the efficiency of the model would also be increased. Weka 3.6 software was employed for all the tests that were conducted. The optimal performance was achieved when eight attributes were used in addition to the class containing missing values being removed. The Bayesian networks algorithm, which achieved optimal performance among all the algorithms tested in this paper, was able to achieve an accuracy of 97.80% in its best configuration.

Al-Hadidi et al. [36] proposed a novel kNN ML approach to more accurately detect breast cancer. They designed a method consisting mainly of two parts: the initial part of the approach processed the images received as input for feature extraction, while the second part consisted of the extracted features that were processed using the two models, one of which was a neural network and the other model employed logistic regression. Further, they compared both models and analyzed them using the Matlab software. During the study, the reported error value was < 0.07, and the neural network-based model made use of a fewer number of features compared to the one that used LR. Although the number of features consumed by the BPNN model was 24 less than the LR-based model, they were able to obtain a success rate $> 93\%$ using that model. Sinha et al. presented their work on employing an ML-based approach for the early diagnosis of breast cancer [59], wherein they used ML methods to analyse the number of cancer patients with tumours and present a report on the same. There were 567 rows of data representing 30 distinct attributes of breast cancer traits in the Breast Cancer dataset used by the authors. The rows containing information about the nature of the tumour (i.e., benign vs malignant) were taken out and set as target attributes. Based on the data collected, a percentage was calculated to represent patients with tumours, and the predictions were presented using illustrative visualizations. To obtain unbiased estimates, the researchers used supervised ML algorithms. Based on the testing results, they found the K-Nearest Neighbours to be the most accurate predictor with an accuracy of 91.6%. The least accuracy was displayed by the NB approach, which showed an accuracy of 75.6%, while the kNN-based approach showed an accuracy of 90.9%, which was the highest among the lot.

Gayathri and Sumathi [60] presented a comparative analysis for the RVM algorithm, which brought forth considerably lower computational costs when pitted against other algorithms that were also utilized for breast cancer diagnosis. The study evaluated how the RVM approach provided an edge to correctly diagnose breast cancer even when the features were reduced over other ML models. The RVM was compared against ML algorithms like Naive Bayes, neural networks, DT, SVM, and Fuzzy inference systems for performance analysis. The study showed that RVM performed significantly better over the other models. Previous studies showed that an RVM-based approach had rarely been used for the WBCD dataset for diagnosis of breast cancer, but was more widely accepted for other types of cancers such as blood cancer and lymphatic cancer. Hence, Gayathri utilized the original WBCD in their study to detect breast cancer, which outperformed all the other approaches of the time and displayed an accuracy of 97%. Even when the features (variables) were reduced, RVM still showed better performance than others. Still, the study stated that there was scope for improvement in the future and suggested that it could also be fused with other ML algorithms to further increase the accuracy by fine-tuning. Karabatak presented a novel classifier based on Naive Bayesian for diagnosis of breast cancer. Naïve Bayesian, which is based on the Bayes theorem, is an uncompli-

cated classifier [61]. The experiments presented in the study were discerned by using a *k*-fold cross-validation test. In the first step, the input data was randomly divided into five parts and for every computation, one was used as the test data set and the other four were marked as the training dataset (80:20 split). The most significant advantage of the method was that it was irrelevant to the predictions in what manner or order the data were divided. Several techniques for performance evaluation were also used. The outcome showed a sensitivity of 99.11%, accuracy of 98.54%, and specificity of 98.25%. As shown by the results, it was proven that the weighted NB approach outperformed the regular NB and several other models as well. Owing to the grid search methodology used in the model, NB had certain drawbacks like being computationally expensive. The authors suggested that these shortcomings could be further investigated and improved upon with the help of genetic algorithms.

Celik et al. [62] presented a paper on the early detection of breast cancer by using four ML algorithms that were applied on data retrieved from blood analysis. The study aimed to compare four algorithms and analyze the outcomes of the ML models. The methods used were *k*-NN, ANN, SVM, and Extreme Learning Machine. Hyperparameter tuning and optimization were also used to boost the results of the classification. The main advantage provided by this hyperparameter optimization was that it affected the accuracy of the system based on the number of hidden layer neurons and the range of these ranges could be manually tuned by the user. The highest level of accuracy was shown by the ELM model that displayed an average accuracy of 80%. The optimal number of hidden neuron layers was found to be 1800 as a result of the various tests conducted. The use of standard ELM is more advantageous in terms of accuracy. Mojrian presented a paper on the hybrid ML model for diagnosis of breast cancer that was based on a Multilayer Fuzzy Expert System [63]. The ELM-RBF model uses a classifier known as ELM or Extreme Learning Machine, combined with a radial basis function kernel—an RBF. These authors also used WBCD. Several evaluation metrics were established for analysis of the said model. These metrics comprised the MAPE, RMSE, confusion matrix, R2, and k-fold cross-validation ($k = 10$ in this case) methods. After thorough testing, an average accuracy of 98.05% was achieved by this hybrid ELM-RBF model with the help of a 10-fold cross-validation technique. However, at the same time, a linear-SVM model only showed an accuracy of 90.56%. The results obtained by the implementation and analysis of the hybrid ELM-RBF model proved that this hybrid model outperformed the linear-SVM in almost every field, and the accuracy obtained with the hybrid model was also significantly higher than that of the linear-SVM one.

Jeeva et al. [64] analyzed breast cancer detection, classification, and detection capabilities using image processing. In their study on image processing, the image was pre-processed before being utilized to discard the redundancies present in the input images without affecting the final product images. The proposed method used the discrete wavelet transform (DWT) coefficients as a feature vector and used SVM and ANN algorithms. Images of patients with medical conditions have been processed with the wavelet, the powerful mathematical tool for feature extraction, to calculate DWT coefficients. Wavelets are especially useful for classification because they provide information about the frequency of a signal by providing localized information. The accuracy was reported as 99.51% for SVM and 98.54% for ANN. One of the limitations of ANNs is the difficulty in obtaining accurate results. Thus, multiple images to detect breast cancer in a short time cannot be analyzed with this method. In the beginning, pre-processing is done. Changing the dimensions, resolution, and contrast of the training and input images helped arrange all the images in the same proportions without affecting the details. By using the DWT method, various parts of the image can be identified for feature selection. A grey image is produced after feature extraction, with pixel parameters ranging from 0 to 255. To identify differences, we used SVM to segregate the breast cancer samples into two groups-those affected by cancer and healthy breast tissue. A feature extraction and image processing technique that aids radiologists in detecting breast cancer is used by Jeeva et al. to detect it at an earlier stage with greater accuracy. In 2021, using deep learning, Amit et al. [65] presented a method to detect breast cancer by classifying thermographic images. A CAD method was proposed to identify three distinct case scenarios under database management: cancerous, non-cancerous, and no cancer. Among the most well-known applications of thermography are screenings for breast cancer. However, thermography is not yet proven to be the ideal method for CAD application. Additionally, doctors prefer thermography results over mammography results because thermography is safer than mammography. Thermal imaging breast cancer screening can replace other forms of breast cancer screening if it is improved sufficiently. According to this study, thermographic testing and treatment should be performed using a CNN, which addresses the disadvantages mentioned above. In this study, an effective and accurate technique for segmenting thermograms and detecting breast cancer is proposed so that it can be categorized as normal or pathological. To produce clear and distinct images, pre-processing is critical. First, data augmentation is performed. This step contributes to increasing the size of the dataset by applying multiple conversions to the original input. Translations, symmetries, and rotations were used to repeat the input. Below are the steps involved in pre-processing augmentation: (1) Translation – An image can be rendered in a particular direction with a certain number of pixels. (2) Centring-each row and column was cut-off at the sides. Consequently, a variety of sizes of photographs were obtained. After cropping all rows and columns, the number of images is counted. Before being resized, the files are levelled into a single size. Based on transparency, randomized images for healthy subjects and patients with cancer are selected after pre-processing. The CNN algorithm overall performs very well in this experiment, with a 99.65% accuracy and an overall 0.0067% loss of accuracy while training the model. On the same dataset, the accuracy of the random forest and SVM algorithms were examined and their results were 90.55% and 89.84%, respectively (Table 1). By segmenting thermographic sinus images, a novel region of interest (ROI) was introduced. By generating representative data sets based on experts' images and providing input to CNN, ground-truth images were used for the ML training. Additionally, future studies should aim to provide a scientifically valid method for evaluating these findings.

Among all the papers we examined, the ML models that performed relatively the worst were models using the NB algorithm. At the same time, our tests revealed that the most robust performance and the highest level of accuracy in the early diagnosis of breast cancer were achieved with the help of a custom ML model that used the fuzzy ELM-RBF algorithm [63]. Statistics showed that this model had an average accuracy rate of 98.05%. A variety of algorithms and ML models are currently available that can achieve the same goal. However, it can be observed that the best results are obtained whenever two different algorithms are fused into one, highlighting the advantages of both models and diminishing the limitations, as seen in this model. One of the main applications of this model is that it helps to almost eliminate the need for sampling from patients, with high accuracy, and process the results; this helps to reduce the cost of the medical procedure. This also helps avoid all major complications involved with the procedure. Thus, this model [63] not only provides the highest accuracy in breast cancer detection but also has further applications and implications for the entire medical field. Moreover, this model can be modified for other types of cancers with little-to-moderate effort.

5. Biosensors using breast cancer detection

Biosensors have been developed as a means of testing for bioanalytical molecules in the areas of engineering, biology, and chemistry [21-22]. Biosensors have two main components: (1) a transducer that converts biochemical response into measurable output signals, and (2) a bioreceptor on the sensor to capture the matching sample [22]. Biosensors work in a way that can indicate the presence of abnormalities within

Table 1 Comprehensive study on breast cancer detection using machine learning

Machine learning algorithm	Dataset	Database	Accuracy (%)	Limitations
Decision Tree J48 algorithm [66]	Wisconsin	Digitized images of FNAC of a breast mass	94.56	Due to the data mining process being used to collect data, additional prognostic factors need to be explored from a more recent timeframe and be added to the decision tree.
Gaussian Mixture Model (GMM) [67]	DDSM	Scanned film mammog-raphy	86	It provides worse results when detecting benign tumours than the SVM classifier.
k-Nearest Neighbours classifier (k-NN) [68]	Thermograms from Federal Fluminense University Hospital	Breast infrared images	94.44	This study does not use a thermographic database to store and evaluate normal and abnormal images, leading to suboptimal results.
Genetic algorithm (GA) optimized artificial neural network (ANN) [69]	MRI from radiologists of the University of Bari Aldo Moro	MR Images	89.77	The entire part that begins with MRI acquisition and ends with lesion classification is not currently automated here during the phases of MR analysis.
k-Nearest Neighbours classifier (k-NN) [70]	Wisconsin	Digitized images of FNAC of a breast mass	95.90	KNN is expressed as a non-parametric ML algorithm, whereas an NB algorithm can be expressed in either non-parametric or parametric terms.
Sequential Minimal Optimisation(SMO) [71]	Wisconsin	Digitized images of FNAC of a breast mass	96.99	–
Artificial neural network (ANN) [72]	Department of Obstetrics and Gynaecology of the University of Coimbra (CHEA)	Data collected by using blood analyses.	86.95	The size of the dataset used was quite small (116 instances) so might have fewer chances of being accurate in the real-world data.
Support Vector Machine (SVM) [73]	Wisconsin	Digitized images of FNAC of a breast mass	94.3	Convolutional neural networks (CNN) provides better accuracy for mammogram-based detection.
Fuzzy ELM-RBF [63]	Wisconsin	Digitized images of FNAC of a breast mass	98.05	–
Deep neural network with Support Value (DNNS) [74]	M. G Cancer Hospital & Research Institute, Visakhapatnam, India	Histopathology image samples	97.21	Because of the small size of the dataset, it needs to be enlarged using data augmentation.

the human body by detecting certain biomarkers within the human body. By definition, a biomarker is a molecule found in blood, tissues, or other body fluids that can be an indicator of normal or abnormal process, a condition, or a disease. Recent research on biomarkers has indicated their significance in the detection and treatment of a variety of cancers. Tumour biomarkers are considered the most valuable among other biomarkers [26]. Since the first tumour biomarker was discovered in 1847, more than 100 tumour markers have been discovered over the past two centuries. Many of these markers are found in the bloodstream and provide vital information about a person's health. The two main biomarkers relevant to breast cancer are protein-based biomarkers and gene markers [75]. Various kinds of biosensors, DNA-based sensors, and other technologies for breast cancer detection have been developed over the years. Given their advantages over others, electrochemical biosensors have garnered greater interest and are widely used. The highly sensitive, miniaturized design, simplicity, and low cost of electrochemical biosensors are their main advantages [39–41]. They offer elegant approaches to interfacing, including signal-transduction and DNA recognition, by which the focus is on the directionality of electrical signals generated by hybridization DNA probes and target DNA [39, 41].

Gohring et al. [76] presented a study for the diagnosis of a breast cancer biomarker, HER2, (in human serum samples) by applying a label-free approach with an optofluidic ring resonator. This study was aimed at developing a low-cost detection system that could be used to monitor disease progression using HER2 proteins detected in the serum at varying concentrations. Based on the opto-fluidic ring resonator's (OFRR) results, serum samples were detectable at medically relevant concentrations of HER2 in a short span of 30 min (detection range: 13–100 ng/mL). HER2 biomarker measurements show that the bulk refractive index sensitivity for the OFRR was found to be 30 nm per refractive index unit (RIU). The OFRR was tested with ethanol, passing through it at increasing concentrations of a known refractive index, to determine its sensitivity. With this device, one can assess the clinical prognosis of patients with improvements in accuracy and monitor the effectiveness of treatment at a low cost.

Gruhl et al. [77] presented an article on the use of an acoustic biosensor to detect the biomarker indicative of cancer, HER-2/neu, by using a label-free approach. An embedded surface acoustic wave (SAW) device was used in a flow cell to develop a novel biosensor system for the flow injection analysis (FIA). To develop a procedure that allowed the directed orientation of the capture antibodies, two biotinylated molecules—neutravidin and biotinylated protein A—were used to assemble the linker system. Extracellular domain (ECD) of HER-2/neu (HER-2/neu-ECD), a clinically relevant protein marker, could be detected with this technique at a concentration of about 10 ng/mL. For diagnostic applications, the cut-off value was 13–20 ng/mL. Based on published literature, the surface modification was designed for low concentrations of HER-2/neu-ECD. They developed an efficient coupling process that could accommodate both anti-HER-2neu and anti-HER-2neu-ECD, the latter of which is a potential biomarker for breast cancer. Because antibodies are widely used in the biotechnology industry as binding molecules in binding assays, the findings may be useful for other principles and applications of biosensors in clinical diagnosis.

Rafiee-Pour et al. [78] presented a novel electrochemical miRNA biosensor that used a label-free approach that employed a redox indicator, methylene blue (MB). The biosensor may be applied to the breast cancer biomarker miRNA-21. The main concept in this study was to determine miRNA without excessive labelling or operational complexity. In consequence, a detection limit of 84.3 fM which is considered relatively low, can be achieved with this strategy, thus making it possible to detect miRNAs at concentrations from 0.1 to 500 pM. This study used a comparison of the proposed miRNA biosensor on perfect complement and mismatch targets to determine its selectivity. With the same concentration of 200 pM, the electrochemical signal of the miRNA-21 (complementary target) was significantly larger than the current from the miRNA-192 (non-complementary sequence). Using MB as a hybridization indicator, a novel platform for sensitive detection of miRNAs was developed in this work. MB was used to measure the miRNA-21 concentration by determining the difference in oxidation peak current between the DNA or duplex DNA/miRNA. Therefore, these results indicated that the electrochemical miRNA biosensor is a highly effective biosensor with the following notable advantages: fast, low cost, simple preparation procedure, wide linear range, and relatively rapid production.

It is crucial to detect breast cancer early and boost patient survival rates. Arif et al. [79] reviewed a device designed for self-screening as well as early detection of breast cancer. Their paper describes the design of a small device that can be placed and used at home. The process utilized several components like salivary autoantibodies, breast-cancer specific biomarkers, and biosensors to detect the cancer at an early stage by measuring the concentration variation of a biomarker in saliva. Autoantibodies present in the saliva can be detected early and lead to precise detection of different cancer types. There is evidence in the literature that autoantibodies against ATP6AP1 or other autoantigens begin to surface in the initial stage of a disease, and could be used as potential biomarkers to diagnose the disease early. There is an increasing reliance on saliva as a detection medium of choice. Using quartz crystal microbalance biosensors to detect autoantibodies against ATP6AP1 in saliva, the study provides information on the sensitivity of this detection technique. A prototype could also be made of the device. However, concerns about the saliva containing enough ATP6AP1 autoantibodies need to be addressed to validate the specificity of disease detection.

Jabin [80] presented an article on biosensors with titanium coating for cancer cell detection based on surface plasmon resonance technology. Basically, the goal was to develop a sensor that could achieve a greater sensitivity towards amplitude, wavelength, and birefringence. One of the major objectives of the proposed cancer sensor was to define the light absorption characteristics of a desired biosample by means of plasmonic resonance, and ultimately assist in the detection of cancer using a real-time finite element method (FEM) approach. Displaying a coupling length all the way up to 66 m, the sensor exhibits a high birefringence of 0.04, so it can provide information that will be valuable for both science and engineering. However, with a resolution ranging between 1.5×10^{-2} RIU and 9.33×10^{-3} RIU, the optimal wavelength sensitivity in the proposed structure ranges between 10,000 nm/RIU and 17,500 nm/RIU. Depending on the type of cancer cell, the transmittance variance of ranges between 3300 and 6100 dB/RIU, and the amplitude sensitivity for major polarization mode is between -340 RIU^{-1} and -420 RIU^{-1}, ensuring a detection limit that can reach up to 0.025 in a state of major polarization. Additionally, the sensitivity of this biosensor is measured through comparison to other structures influenced by similar data, and this makes it one of the best structures proposed so far. The proposed model features enhancements to the previously described D-shaped photonic crystal fiber (PCF) that allows for greater flexibility in terms of the optical parameters and a noticeable improvement in their sensing capability.

Graphene's excellent mechanical and electrical properties make it particularly suitable for breast cancer field effect transistor (FET) biosensors; hence, graphene-based materials have become popular for this application. There is a wide array of biosensor materials that are either made purely of graphene or have a certain concentration of graphene in their composition, which contains single to few-layer pristine graphene, nanoribbons, graphene oxide (GO), reduced graphene oxide (rGO), doped graphene, and even "damaged" graphene. Novodchuk et al. [81]. presented a review to highlight the progress made in graphene-based functional electrochemical sensors for bio-sensing of breast cancer cells and compared them to previous graphene-based biomarkers, biosensors, and device configurations. It has been observed by analyzing several biosensors that increased electrical properties and mobility significantly increase the sensitivity of the biosensor. Further, the threshold limits of current top-of-the-line devices were compared for multiple analytes, current ratios, and the mobility for each device. Various biomarkers are often targeted by different bioreceptors to perform selective detection in a bio environment. In addition, size is an important characteristic of a bioreceptor material, as it is typically limited by its Debye screening length when it is an FET biosensor.

Shafiei et al. [82] presented a reduced graphene oxide-chitosan-gold composite-based electrochemical aptasensor that allows for the detection of breast cancer cells without the use of labels. The authors aimed to detect cancer cells (MCF-7) with an ultrasensitive aptasensor. The composite they used was made from reduced graphene oxide, chitosan, and gold nanoparticles on the electrochemical biosensor surface to improve the detection limits and signal enhancement. Furthermore, an aptamer for nucleolin, AS1411, was used as a biosensor recognition element, which is an overexpressed protein present on the surface of cancer cells. The aptasensor demonstrated a wide linear range 10–1,000,000 cells/mL, a confirmed limit of detection of 4 cells/mL on the lower side, and a linear correlation with the mathematical logarithm of the cell concentration. The aptasensor fabrication process was studied by electrochemical impedance spectroscopy and cyclic voltammetry. As a result of the higher concentrations of cells, those cells were more likely to be captured by the aptasensor that blocked the access of ferro/ferricyanide to the sensor, increasing the charge transfer resistance. Thus, this aptasensor identified MCF-7 cancer cells with high efficiency and without the presence of an electrochemical or optical label. Using this simple and highly sensitive aptasensor, one can accurately distinguish healthy cells from cancer cells.

Mansor [83] studied an electrochemical DNA biosensor with embedded nanowire made out of zinc oxide with the goal of detecting the *BRCA1* gene. Research conducted in this study focused on showing that nanowires of zinc oxide fabricated on gold surfaces can be an appropriate platform for the development of biosensors capable of detecting *BRCA1*. Demonstrating a 3.32 μM detection limit, the proposed DNA biosensor was capable of detecting the target sequence at concentrations ranging between 10.0–100.0 μm. Field emission scanning electron microscopy (FESM) images showed that the nanostructure grown on the gold electrode had a mean diameter ranging from approximately 450 to 550 nm. Tests with the electrodes prepared with ZnONWs/Au showed that the electrodes are ideal for DNA immobilization. Additionally, DPV measurements were used to determine direct electrochemistry of DNA, allowing them to identify the *BRCA1* gene by detecting short DNA sequences when DNA probes were chemisorbed onto the ZnONWs/Au surface. As a consequence, a satisfactory surface oxidation peak was observed at about 0.8 V in the presence of complementary DNA sequences. It was found that the optimal pH for DNA biosensors was at pH 7. Therefore, this technique can be carried out on real breast cancer cells using more complex array formats for the detection of genes such as *BRCA2* and *p53* among many others. Hossain et al. [84] were the first to demonstrate a numerical model of a hybrid SPR biosensor utilising graphene coating and fibre-optic surface for the detection of *BRCA2* (breast cancer gene 2) and *BRCA1* (breast cancer gene 1) genetic breast cancer. The objective of their study was to present the numerical modelling of the biosensor for detection of breast cancer involving two specific mutations found in the *BRCA1* and *BRCA2* genes—916delTT and 6174delT, respectively. This study analysed performance in terms of sensitivity and open windows toward early detection of genetic breast cancer that was derived from *BRCA1* or *BRCA2*. The quantification results showed that graphene had an approximately 35% higher sensitivity than the usual surface plasmon resonance (SPR) biosensor most likely owing to graphene's absorption ability. Sensors such as these, when used to detect tumour cells, provide an easy and convenient method for the identification of specific mutations in the genes *BRCA1* and *BRCA2* genes. By examining the variation in SRF and SPR angles, the sensor can distinguish between the matched DNA interactions from mismatched DNA interactions that take place between the p-DNA, a sh-DNA mutation type, and the target DNA (a mr-DNA mutation type). As a result of graphene's prominent properties, it is placed between the gold film to serve as a medium for the efficient absorption of light. Early breast cancer can be detected using DNA hybridization event analysis on the basis of four key factors—reflectance, maximum transmittance, SRF angle, and SPR angle. Its improved sensitivity makes the proposed hybrid SPR biosensor ideal for future applications in early breast cancer detection based on the genetic biomarkers 916delTT and 6174delT.

Li et al. [85] used an electrochemical-based approach for the detection of breast cancer cells. Using two sets of tumour markers to-

gether on the surface of the cells, the main objective and aim of this study was to detect breast cancer cells. Observations from the experimental results showed that only under special conditions could both tumour markers be detected on the tumour cells' surface, along with a satisfactory electrochemical response. MCF-7, a cell specific to breast cancer, can be differentiated from several other types of cells if this method is used. Further, the prepared cytosensor has good reproducibility and a low detection limit for MCF-7 cells at a number of concentrations between 10^{-4} and 10^{-7} cells/mL with possible medical applications. Breast cancer cells were screened by using a method to simultaneously detect MCF-7 and CEA on their outer surface of cancer cells. With the ability to measure cancer specifically, systematically, and cost-effectively, this method offers great promise for fast, simple, and reproducible cancer detection. Benvidi et al. [38] designed an ultrasensitive and highly selective electrochemical DNA biosensor that could detect breast cancer in its preliminary stages. The authors' aimed to report a new type of electrochemical biosensor for detecting breast cancer-associated genes such as *BRCA1*, by using a gold electrode via electrochemical impedance spectroscopy (EIS), cyclic voltammetry (CV), and differential pulse voltammetry (DPV) methods. A comprehensive electrochemical redox study was carried out with ferricyanide and ferrocyanide as an electrochemical redox couple after the construction process was explored using CV and EIS. An electrochemical biosensor based on EIS displayed a wide dynamic range (1.0×10^{-19} to 1.0×10^{-7} M) under optimum conditions and a low detection limit (4.6×10^{-20} M) for the target DNA as opposed to the DPV technique, which has a detection limit of 2.5×10^{-15} M for a linear range of 10^{-14} to 10^{-7} M. On the basis of breast cancer data acquired from GenBank, particular primers and probes were modelled. Because of the ability to detect *BRCA1* at extremely low levels, this study proves that the proposed biosensor can successfully identify *BRCA1* in the earliest stages.

Cardoso et al. [86] presented a novel design for biosensing and designed a highly sensitive electrical biosensor to detect the presence of miRNA-155, which had a linear response down to the attomolar range. Their main aim was to develop a simple and inexpensive solution with a concurrent approach design, use a rendering of the serum samples, and minimize the complexity by optimizing the critical variables. The resulting biosensor showed efficiency in detecting miRNA-155 at concentrations as low as 5.7 aM with a sensing range of 10 aM to 1 nM. Selectivity was high towards bovine serum albumin (BSA) and breast cancer antigen CA-15.3. The biosensor response against miRNA-155 was not affected by the raw fluid extracts obtained from melanoma(skin cancer cells), but a positive signal was obtained when extracts from breast cancer cells were at play. The biosensor was constructed by immobilizing the anti-miRNA-155 on a gold screen-printed electrode (Au-SPE) and using mercaptosuccinic acid to clog the non-specific sites. Surface modification of these devices was confirmed by atomic force microscopy and electrochemical methods such as square wave voltammetry, CV, and EIS, which were also able to hybridize with miRNA-155 while still maintaining their stability. This simplistic and robust strategy could prove to be an efficient method for the simultaneous quantitative analysis of multiple miRNAs 155 in physiologic fluids, for POC diagnosis as well as various other biomedical research. Hakimiam and Ghourchian [87] presented a study on highly sensitive electrochemical biosensors for the detection of microRNA-155 as a risk factor for breast cancer. Recent studies in the field suggested that the concentration of miRNA-155 (miR-155) in the human body is directly related to breast cancer. The main objective was to assess miR-155 and analyse the significance of its impact on the presence of breast cancer in an individual, by developing and reporting an electrochemical biosensor that can outperform others in terms of detection speed and sensitivity. Two sequences, namely a three-base mismatched miR-155 and a standard miR-155, were used for the study to determine the specificity of the biosensor. When the biosensor responses in the two scenarios (with and without the use of the two sequences) were compared, it was found that miR-155-induced biosensor responses were almost double those of miR-155 derived from the three-base mismatch miR-155. Thus, the observation of the differences between the two responses suggested that the probe/miR-155 had a higher chance of duplex formation than the probe/three-base mismatched miR-155. Cyclic voltammograms were generated, and the mean value (dl) for miR-155 was 0.70 ± 0.01; the three-base mismatched miR-155 showed a mean value of 0.56 ± 0.08. The introduced biosensor used an ultrasensitive method which displayed a detection limit of 20 zmol displaying a linear range of 2×10^{-20} to 2×10^{-12} mol for the detection of miR-155. The electrochemical biosensor introduced in the report used polyethyleneimine-silver nanoparticles as a redox-active indicator. The result of electrochemical biosensor analysis of the serum samples showed high sensitivity and cost-effectiveness.

Freitas et al. [25] presented a study on the detection of HER2-ECD breast cancer biomarkers using electrochemical sensing platforms. They studied the electrochemical composition of HER2 with the objective of early detection of breast cancer by screening and electrochemical analysis. Briefly, 7.5–50 ng/mL linear calibration plots were obtained and the assay took 2 h and 20 min to be completed. During this time, the limit of detection (LOD) of 0.16 ng/mL (from SPCE-MWCNT/AuNP) and 8.5 ng/mL (from SPCE-AuNP) were obtained and these concentrations were smaller than the established threshold of 15 ng/mL for this specific cancer biomarker. The following sensing platforms were used to detect HER2-ECD: gold nanoparticles-modified SPCEs, graphene, SWCNT, multiwalled carbon tube, and hybrid graphene-modified SPCEs. The SWCNT or MWCNT fused with gold nanoparticles, formed hybrid nanostructures. Based on the analysis of other biomarkers and spiked human serum samples, the platform's applicability was confirmed and its selectivity was determined. In this manner, the developed HER2-ECD detection strategies would be a viable alternative to the conventional way of analysing the *HER2* gene. Salahandish et al. [88] presented an article on nano-biosensor for ultrasensitive detection of breast cancer based on *HER2*. The objective was to design a biosensing system with a high-performance linear response and selective performance with a large linear response range. They created a sandwich structure of a Ni-doped graphene (NFG)/AgNPs/PANI multilayer structure. This structure showed excellent conductivity and stability and allowed increased anchorage of HER2 antigens from cancer cells, which was made possible due to the nanocomposite components being arranged in the proper combination and order. The sensor displayed a rapid response time of 30 min, and an average detection limit of 2 cells/mL for detecting SK-BR3 cells between 10 and 5×10^6 cells/mL. The nano-biosensor demonstrated high sensitivity and specificity with a detection efficiency > 90% for cancer cell detection by using a label-free approach in whole blood samples without sample preparation or the need for staining. The authors also developed ultrasensitive nanocomposites for detecting breast cancer cells with the help of economical AgNP and optimised the methods for nanocomposite synthesis and functionalization. Consequently, their results showed that the new and optimised nanocomposite has potential applications in electrochemical biosensing and super capacitances.

In 2019, Kim et al. [89] presented a study focused on a label-free surface-enhanced Raman spectroscopy biosensor to detect breast cancer in real-time using human tears. At that time, there was no practical sensor that could balance signal enhancement, reproducibility, and uniformity. They demonstrated the use of a Raman spectrometer to estimate or detect asymptomatic breast cancer by utilizing human tears and combining a multivariate identification algorithm based on multivariate statistics to demonstrate feasible practical applications. Mucins, glycoproteins, non-glycosylated proteins, peptides, and lipids could be found in tears, making them a special source of body fluids. Tears are a good source of biomarkers, because they can be collected noninvasively, do not contain many solid proteins such as albumin, and do not require further purification. By analysing human tear fluids for breast cancer, they evaluated the feasibility and versatility of the Au/HCP-PS monolayer as a biosensor. PC-LDA identification using leave-one-out cross-validation

(LOOCV) provided 96% classification accuracy. Tear-fluid-based asymptomatic breast cancer detection achieved 92% clinical sensitivity and 100% specificity. It is anticipated that if appropriate sensitivity is guaranteed, the new diagnostic method will overcome the shortcomings of conventional labelling techniques, such as high costs and low yields. In these studies, the non-invasive, label-free, real-time screening technology was found to be effective at detecting asymptomatic cancers early, reducing the likelihood of recurrence. By the end of 2020, Abrao Nemeir et al. [90] developed a new method of detecting HER2 in saliva, a better alternative to blood, by using EIS. The current detection method of HER2 remains highly specialized, costly, and time-consuming, given the difficulty in using biosensors for low concentrations. With label-free electrochemical biosensors, the goal is to detect HER2 in saliva at a low cost. The detection produced a biosensor that is highly linear, sensitive towards HER2, twice as sensitive as HER3, and four times more sensitive than the EGFR interference molecule. A standard addition method was used to detect HER2 in real saliva, which proved to have good linearity ($R^*2 = 0.9904$), hence proving that this technique could be used to detect HER2 in real patients. In this method, a diazonium salt was initially deposited on the SPE by means of cyclic voltammetry. Later, the anti-HER2 antibodies were immobilized using 1-ethyl-3-(3-dimethylamino) propyl carbodiimide/N-hydroxysuccinimide. In a microfluidic system, electrochemical impedance spectroscopy was used to detect HER2 biomarker concentrations. In its physiological concentration range of 5–40 pg/mL, the biosensor showed a higher linear detection of HER2. With the standard addition methods, the biosensor was used to detect HER2 concentrations of up to 10 pg/mL in real saliva. Hence, this method of diagnosis has proven to be highly effective and efficient on real patients, which means it can be used instead of conventional methods.

During this research, we found that there are various types of biosensors that utilise different biomarkers to detect tumour cells. Others allowed finding specific mutations in biomarkers. We discovered that the biosensor that performed relatively worse was the ZnO nanowires-based DNA biosensor used to identify the *BRCA1* gene with the detection limit of 3.32 μM and a linear range between 10.0 and 100.0 μm [83]. On the other hand, our tests also revealed that the most robust performance, as well as the highest sensitivity and specificity, were observed with an electrochemical biosensor for detecting the presence of miRNA-155 at attomolar levels, during a breast cancer diagnosis. These electrochemical biosensors have a detection limit of 5.7 aM and a linear range of 1–10 aM that was achieved by immobilization of the anti-miRNA-155 in Au-SPEs [86]. Several biosensors of this type are common; however, the aforementioned device can be repeatedly used with subsequent readings, most notably in EIS measurements, and shows high selectivity toward extracts from other tumours and diverse proteins from biological fluids [86]. In addition, this device provides more realistic opportunities for analyzing miRNA cancer biomarkers in a clinical context, as well as allows these markers to be reused because of its de-hybridization properties. Further, reusing it in an online sensor approach (Table 2).

6. Challenges and future scope

The primary challenges around cancer detection and treatment include designing research pipelines, identifying the growth mechanism of the specific cancer type, designing preclinical models, managing complex cancers precisely, early detection, and developing innovative clinical trial methods for enhanced accuracy that could be useful to doctors and patients for early detection and as a second opinion [74]. In order for ML technology to be reliably used for the diagnosis and treatment of cancer, some key challenges must be addressed. It is crucial to extract features from medical imaging data and process them before they can be used as input data. Therefore, medical imaging data cannot be used directly as input data. Along with the development and popularization of technology, the weights of coefficients in neural models are calculated, so a reasonable confidence interval can be drawn, which can lend itself to further medical research [99]. To train the model, the images in the datasets are magnified, but by doing so, the histology images are altered in size that can greatly enhance quality processing during training. Low magnification analysis of the histology images is challenging because the images contain so many tissues. Learning discrete features from an image at multiple magnification levels can be beneficial to make a distinct and accurate diagnosis, but is quite challenging at the same time [5]. Heterogeneous breast densities make mass detection and classification more challenging than calcifications. Traditional ML methodologies present confined approaches that only operate on a specified density type or dataset [74]. In ML applications, one of the biggest biological challenges in constructing efficient and accurate classifiers that are suitable for practical use. It is predominantly the following challenges in gene expression classification that are of concern: the huge number of gene expressions, investigation of relevant features, the existence of noise in the datasets, and accuracy as well as reliability of classifications. Major future trends in computational biology designed to check for breast cancer recurrence may get good results by using a combined effort of different recent ML techniques and findings from cancer researchers [100]. Large epigenetic datasets need to be made publicly available and more accessible for novel ML approaches to be properly developed, improved, and tested. Despite improved technologies, there is room for improvement in accurate cancer detection, characterization, and monitoring. The ability to make clinical decisions is dependent on the accurate diagnosis of the disease. There is a great need for reliable tracking of neoplastic diseases over time as due to certain treatments certain surrounding tissues are affected. Due to this, the surrounding tissue may acquire signal characteristics that are difficult to distinguish from the tumour [101].

Diagnosis of younger women is more difficult than that of older women owing to the higher breast tissue density of the former group. In previous models, the detection of one cancer cell was based on the performance of the neighbouring cancer cells. A cancerous cell could only be evaluated in relation to another cancerous cell. The use of biosensors for cancer detection in the future shows great promise. Biosensor design poses the challenge of storing and processing biological samples, as they are highly perishable and must be stored before testing. Furthermore, some biomarkers are less specific and are apt to serve as markers for more than one type of cancer. It is possible to solve this problem by using a biosensor-based platform that is capable of detecting multiple biomarkers simultaneously and exhibiting high sensitivity and specificity. miRNAs regulation is different in patients compared to healthy individuals. The data suggest that miRNAs in the body can serve as effective biomarkers for diagnosing and tracking cancer. However, circulating miRNAs continues to be challenging to detect without prior extraction and purification [93]. Despite the low detection level, miRNA modification requires professional operation like purification and exact working conditions for real-time sample determination, which may impose some difficulties. In spite of the significant advancement in cancer diagnosis owing to research around tumour markers, current diagnostic procedures are invasive, uncomfortable, and inconvenient, and these issues need to be addressed. Therefore, the discovery of non-invasive biomarkers for the early detection of cancer is of great importance [94]. An important challenge in electrochemistry is how to bring the technology to the patient in an accurate and reliable manner without compromising accuracy or reliability. It would therefore take a great deal of developmental work to realize decentralized electronic cancer tests. Innovation in the field of sensing has made electrochemical devices widely applicable in clinical settings. These devices may be particularly suitable for providing information in a straightforward and rapid manner at a lower cost, making them uniquely suited for point-of-care cancer screening [39]. Despite their promising capabilities, the electrochemical biosensors that will determine circulating biomarkers of breast cancer are still in the early design stages or prototype stages at best, and none of them has been tested with a large enough patient population to demonstrate their reliability in clinical practice. This problem

Table 2 Comprehensive study on cancer detection using biosensors

Name of biosensor	Biosensor specification	Analyte	Performance	Linear range
FET biosensor [91]	Transducer rGO-Encapsulated SiO_2 NPs	HER2	The detection limit is 1 pM Mobility is 3 $cm^2V^{-1}s^{-1}$	1 pM to 1 μM
Electrochemical [92]	Hemin/miR/DNA-Au/probe/AuNPs/Au electrode	miR-21	Detection limit is 6 fM	0.01–500 pM
Electrochemical [93]	Two auxiliary probes that self-assemble to form 1D DNA concatemers	miRNA 21	LOD is 100 aM	100–10^5 aM
Electrochemical [94]	P19 captured dual aptamer complex on SPCE	miR-205	Detection limit is 0.6 nM	2–10 nM
Electrochemical (EIS) [95]	Aptamer on a gold electrode and iron redox probe readings	Progesterone (PR)	LOD is 0.90 ng/mL Response time: 40 min	10–60 ng/mL
Electrochemi-cal [96]	Anti-miR probe/GNR/GO/GCE	miR-155	Detection limit is 0.6 fM	2.0 fM to 8.0 pM
Electrochemi-cal [86]	Immobilization of anti-miRNA-155 on Au-SPE	miRNA 155	LOD is 5.7 aM	10–10^9 aM
Sandwich electrochemi-cal biosensor [13]	polydA-aptamer-modified gold electrode polydA-aptamer functionalized gold nanoparticles/graphene oxide hybrid	MCF-7 cells	The detection limit of 8 cells/mL (3σ/slope)	10–10^5 cells/mL
FET biosensor [97]	Transducer G-graphene/PBASE	DNA	Detection limit is 100 fM Mobility is 64 $cm^2V^{-1}s^{-1}$	100 fM to 1 nM
FET biosensor [98]	Transducer rGO/SA	BRCA1	Detection limit is 0.2 nM	0.2–75 nM

needs to be addressed by testing the methodology on large numbers of real-life samples and comparing it with other competitive approaches [102]. In future, increasingly sophisticated technological innovations in biosensors that incorporate biomarker patterns, software, and microfluidics can make these devices highly effective in this application area [26].

7. Summary

In the past few years, various breast cancer detection methods have been developed by applying ML algorithms and biosensors. In addition, breast screening techniques and Big Data analysis techniques are also increasing over time. Most of the databases require pre-processing dependent on the ML model used. However, there were some differences in performance measuring factors, and the different models use different metric elements depending on the dataset. Whereas, according to its use, biosensors require an analyte that will be used to generate an electric signal to identify biomarkers. Similar to ML inputs, analytes also need to be processed prior to testing. The specification of each biosensor varies according to the analyte used. After carrying out these comparisons and analyzing all the aspects of each ML model and biosensors that are used to detect breast cancer efficiently, we found two optimum techniques, one of each. First, the Fuzzy ELM-RBF ML algorithm was found to be the best model for breast cancer detection with 98.05% accuracy. The WBCD has used digitized images of FNAC analysis of a breast mass. Second, the electrochemical biosensor with a detection limit of 5.7 aM that was used to detect miRNA-155 from serum samples by immobilization of the anti-miRNA-155 on Au-SPE was found to be the best biosensor. The biosensor could detect very low concentrations of miRNA-155, down to 1–10 aM in serum samples. A significant area was analyzed in this research of breast cancer detection at an early stage. Researchers' interest in the field of breast cancer detection is evident from the exponential growth of published research articles on a yearly basis. Analyzing the existing research will enable clinicians to make highly accurate diagnoses, ultimately leading to more effective treatment of patients.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Author contributions

In this paper, Yash Amethiya worked on data curation from various sources. Then after Yash Amethiya and Prince Pipariya did the theoretical performance analysis for different types of biosensors and Machine learning models. Prince Pipariya investigated the data and information. Further, Shlok Patel did the comparative analysis for better insights and again validating the data. Now, the original draft was prepared by all the authors and at last, it was again reviewed by Shlok Patel. Manan Shah has worked on writing and editing part.

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