

MRI radiogenomics for intelligent diagnosis of breast tumors and accurate prediction of neoadjuvant chemotherapy responses — a review

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MRI Radiogenomics for Intelligent Diagnosis of Breast Tumors and Accurate Prediction of Neoadjuvant Chemotherapy Responses — A Review

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Abstract

Background and Objective: This paper aims to overview multidimensional mining algorithms in relation to Magnetic Resonance Imaging (MRI) radiogenomics for computer aided detection and diagnosis of breast tumours. The work also aims to address a new problem in radiogenomics mining: how to combine structural radiomics information with non-structural genomics information for improving the accuracy and efficacy of Neoadjuvant Chemotherapy (NAC).

Methods: This requires the automated extraction of parameters from non-structural breast radiomics data, and finding feature vectors with diagnostic value, which then are combined with genomics data. In order to address the problem of weakly labelled tumour images, a Generative Adversarial Networks (GAN) based deep learning strategy is proposed for the classification of tumour types; this has significant potential for providing accurate real-time identification of tumorous regions from MRI scans. In order to efficiently integrate in a deep learning framework different features from radiogenomics datasets at multiple spatio-temporal resolutions, pyramid structured and multi-scale densely connected U-Nets are proposed. A bidirectional gated recurrent unit (BiGRU) combined with an attention based deep learning approach is also proposed.

Results: The aim is to accurately predict NAC responses by combining imaging and genomic datasets. The approaches discussed incorporate some of the latest developments in of current signal processing and artificial intelligence and have significant potential in advancing and provide a development platform for future cutting-edge biomedical radiogenomics analysis.

Conclusions: The association of genotypic and phenotypic features is at the core of the emergent field of Precision Medicine. It makes use of advances in biomedical big data analysis, which enables the correlation between disease-associated phenotypic characteristics, genetics polymorphism and gene activation to be revealed.

Keywords: precision medicine; Neoadjuvant Chemotherapy (NCT) ; data mining; radiogenomics; Support Vector Machine; Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI); multi-channel reconstruction; self-supervised & semi-supervised deep learning; breast cancer; Computer Aided Classification; BI-RADS; breast density

I. Introduction

Incidences of breast cancer have increased dramatically in the past 30 years, and the peak incidence has gradually shifted from the 40-44 age group in the past 20 years to the 50-54 age group in the last decade. The peak age of onset and the median age of diagnosis have been both increasing over time, suggesting that the incidence rate is increasing with age [1]. In a study on the current status of breast cancer in developing countries, it is found that in order to better cope with the increased incidences of breast cancer, focus must be placed first in addressing the pending problem of late breast cancer diagnosis. Early detection is by far the best option in addressing current short-falls in national healthcare systems and reducing the current high mortality rates.

Due to the difficulty of accurately identifying the types of cancer associated with various heterogeneous lesions in X-ray images, there are still several limitations in the determination of the correct treatment plan by consultants. Patients often also need to undergo through several biopsies and the process of determining the nature of the disease can be a cause of distress, anxiety and physical pain for the patient. In addition, breast cancer is prone to metastasis and recurrence, requiring a stream of diagnoses during the lifetime of a patient.

Neoadjuvant chemotherapy (NAC) is one of the important and reasonably well established treatments for breast cancer. Current research on predicting the efficacy of NAC mainly focuses on detecting the relationship between gene expression of tumor tissue and NAC efficacy. The accurate diagnosis and molecular analysis of breast cancer type via MRIs can significantly improve the accuracy of NAC evaluation.

Breast MRI radiogenomics is rapidly becoming a powerful new tool for precision medicine. It can be key to the establishment of clinical treatment plans and prognosis, which can effectively improve the 5-year survival rate of patients and reduce the mortality rate. Specific biomarkers and molecular subtyping can improve treatment efficacy and improve prognosis of NAC for breast cancer, enabling the development of new strategies for personalized medicine. The first article on radiomics/radiogenomics in breast cancer was published in 2012 [2], and since that time there has been a significant number of publications in the subject. The growing literature on radiogenomics in breast cancer relies almost exclusively on MR imaging [3], in particular on DCE-MR images and the correlation of its features with individual genomic signatures, molecular subtypes, or recurrence scores.

Rapid developments of several sub-fields in medical profession and advances in artificial intelligence with advances in radiogenomics is set to become an important modality in disease management and control, and could play a pivotal role in disease screening, early diagnosis, treatment selection, and prognostic evaluation. After years of development in radiogenomics, there is an ever increasing number of useful databases to consult. Extracting useful structured information from genomics datasets and integrating this to unstructured image information for NAC efficacy prediction has become the biggest challenge in this field.

Therefore, there is significant impetus to develop novel solutions that can comprehensively utilize breast tissue radiogenomics data. At present, there are many emergent commercial solutions for breast cancer screening, such as Tencent Miying, Google AI, IBM Watson Health, etc., but most of them are for imaging or genomics data, and there is no comprehensive analysis of MRI radiogenomics that can provide intelligent solutions for breast cancer diagnosis, considering molecular subtyping for efficacy prediction of NAC with different data structures.

Although dynamically enhanced magnetic resonance imaging (DCE-MRI) of breast tissue is characterized by its high sensitivity, the specificity of the detection is very low. Tissue heterogeneity results in a high nonlinearity in the value of adjacent pixels in the captured images; furthermore, the extracted statistical image variables may be highly correlated, rendering the subsequent segmentation and classification tasks more difficult to perform. Because the level of expression of genes in cells varies, morphological differences across the same tissue may also be observed, this is particularly in the case of tumorous cells. Previous studies have shown that changes in gene expression are always accompanied by changes in the occurrence and development of tumors, and the changes in the expression of different genes are uneven.

Ordinarily, MRI radiogenomics research is conducted under the premise that the benefits from fully exploring datasets with differences between individuals have been considered. The key issues that are addressed include how to use differentially expressed gene datasets by combining their radiomics attributes, how to find effective targets that can more consistently reflect the characteristics of cancer-related tumors and how to accurately predict the efficacy of neoadjuvant chemotherapy in breast cancer patients. Existing radiogenomics analysis methods need to evolve further in order to make full use of the extractable features in these datasets.

The more important question to be addressed is how to fully explore the heterogeneous spatial, temporal, and semantic associative representations in these MRI datasets using multi-dimensional and multi-scale analysis, and how to establish a system that can integrate individualized gene expression differences, while taking into consideration the knowledge that is available from an experienced consultant's cognitive reasoning. Such end-to-end interactive analysis of unstructured image data and structured gene information with hierarchical spatiotemporal representations may actually be achieved by combining geometric algebra transformations and an attention network which enables the fusion of multi-dimensional heterogeneous information into a single classifier framework. This is a novel approach that has significant potential to effectively improve breast tumor diagnosis and provide accurate prediction of NAC efficacy. As part of the above framework, this paper also proposes a new feature representation model for high-dimensional medical imaging based on radiogenomics, which has potential to provide more accurate diagnosis and treatment of breast cancers, to effectively reduce unnecessary biopsies, and to further improve the survival rate and quality of life of cancer patients.

II. Methods

A. Multi-modes of breast MRIs

Magnetic resonance imaging (MRI) makes use of the spin of hydrogen nuclei in the blood which upon excitation return to equilibrium through a relaxation process. Relaxation times are different for different types of tissue or tissues that are tumorous or composed of different types of tumours. The difference in relaxation times is used to form MR images. Compared with other clinical imaging modalities for breast tissue image diagnostics, MRI is characterized by its excellent soft tissue resolution and no radiation damage is associated with X-ray screening [4].

Over the past several years, MRI imaging has benefitted from improvements such as the development of a dedicated breast imaging coil, the introduction of magnetic resonance contrast agents and the development of rapid image acquisition protocols using Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) which is now a well established clinical option. Obtaining image sequences at multiple time points before and after the injection of contrast agent not only improves the spatial and temporal resolution of breast tissue MRI, but also combines morphological information with hemodynamics. The intensity of the MRI signal that changes with time reflects the dynamic enhancement characteristics of the tissue of interest, evaluates the degree of blood flow in the tissue, and reflects the changes in the physiological properties of diseased tissue, so that the diagnostic accuracy of benign and malignant lesions is greatly improved. In the diagnosis and treatment of tumors, relative differences in micro-vessels and micro-circulation between malignant and non-malignant tumor tissues can be used to evaluate disease progression in soft tumor tissue and lymph nodes. The most urgent task is to develop new automated tools to fully use the information extracted by DCE-MRIs to reliably identify a tumor region, analyze its morphological features so as to perform reliable diagnosis and subsequently use such information to prevent the further development of breast disease [5].

Radiogenomics builds models by extracting a large amount of quantitative data from the segmented images, and establishing the association between image features, pathophysiology, and gene expression. In the past couple of years, a large number of studies on radiomics and the efficacy of NAC have shown that radiomics can improve the accuracy and predictive performance of uni-modal or multi-modal imaging. MRI radiomics is the most widely used technique, and the commonly adopted MRI sequences are T2WI, DWI, and DCE-MRI. Compared with the single-sequence model, the multi-sequence MRI model combined with T2WI, DWI and DCE-MRI scan sequences before treatment has shown a higher predictive pathological complete response (pCR) ability that was also associated with a long-time survival benefit [6]. In addition, area under the curve (AUC) of radiomics models could reach a score as high as 0.92, with good performance in differentiating malignant lesions from benign ones [7]. According to [8], the predictive ability of this model for three different pathological subtypes, such as hormone receptor positive/HER2 negative, HER2 overexpression, and triple-negative breast cancer has been shown to have good performance in the cohort of the three MRI image sequences.

B. Molecular Subtype Recognition of Breast Cancer in DCE-MRI radiomics

In recent years, computer-aided diagnosis (CAD) systems are being developed, to assist radiologists to better detect and identify breast tissue lesions and to automatically classify them as benign or malignant [9]. The development of radiomics as a separately recognisable sub-discipline is an important basis for the further development of such CAD systems. Radiomics may extract image features that are invisible to the human eye, and thus escape the physician's attention. Furthermore, certain features are characteristic to specific tumour subtypes or related to particular gene expression changes.

Precise information regarding tumor extent, lymph node status, and multi-focality, is of great importance in breast cancer treatment and prognosis, as well as recurrence prediction [10]. Several clinicians now are more and more accepting that a computer-aided diagnosis system combined with radiomics methods can greatly increase the accuracy and specificity of breast cancer diagnosis, help prevent and reduce excessive mammogram screening caused by false positives, improve the decision-making process about molecularly targeted agents based on genetic mutations, and even capture prognostic information on intra-tumoral heterogeneity in a non-invasive, low-cost, and rapid manner [11].

Compared with traditional breast DCE-MRI and diffusion weighted imaging (DWI), the texture analysis based on DCE or DWI image improves breast diagnostic performance of lesions. For example, based on texture analysis, D'Amico et al. [12] constructed a classification system for the differentiation between benign and malignant lesions of breast tissue with the sensitivity, specificity and accuracy of 100% , 90% and 94% respectively; furthermore, Fusco et al. [13] found that by combining the morphological features of breast lesions with the enhanced scanning dynamics information of the lesion, the accuracy of the differential diagnosis between benign and malignant breast lesions is could reach 91.7%, the sensitivity could reach 92.3%, and the specificity could reach 90.9% respectively.

Sutton et al. [14] combined clinical pathological characteristics of the patient with extracted radiomics characteristics and developed a prediction model using machine learning that allows the classification accuracy of each subtype to reach 89.2% for (ERPR+), 63.6% for (ERPR-/HER2+) and 82.5% for (TN). Their approach achieved an overall prediction model accuracy of 71.2% at distinguishing between different IDC subtypes.

Nowadays, it is becoming more widely accepted that breast MR imaging radiogenomics can better assess the correlations between imaging features and breast cancer molecular subtypes of luminal A, luminal B, HER2, and TN cancer [15-17]. The studies discussed in [16,18-19] demonstrate how functional parameters, when assessed after taking into consideration different molecular subtypes, can significantly contribute to our understanding of tumor patho-physiology thus highlighting the significant potential of radiogenomics in improving breast cancer diagnosis and treatment. In another study also supporting the above view, Fan et al. [20] discussed the relationship between radiomics features based on DCE-MRIs and molecular subtyping of breast cancer, and found that the entropy value associated with the image texture features in DCE-MRI, can be linked to the molecular classification of breast cancer; this was based on the fact that the overall classification performance is high (achieving an AUC value of 0.869), suggesting that computer-extracted high-throughput features have a good prospect in distinguishing between

molecular subtypes. The results of the above studies are very encouraging and are heralding a new era of precision medicine for personalized healthcare.

Receptor status and molecular subtype characteristics can further improve the prediction ability, regardless of the selected classifier. However, due to limited spatial resolution, invasive lobular carcinoma and ductal carcinoma *in situ* (DCIS) is likely to cause a lower intake. The lesion is underestimated, and because of its high radiation dose, it is expensive and difficult to use for routine inspection method to evaluate the efficacy of NAC.

C. Genomics research

Recent advances in genomics research include structural genomics targeted at whole genome sequencing and functional genomics focusing on gene expression and functional identification [21]. The genomic information stored in the DNA is transcribed into RNA and then translated into proteins. Transcriptomics and proteomics are used to perform the mapping between information stored in the genome and expressed in the proteome.

Genomics has significantly benefitted in the past several years from advances in next-generation sequencing technology and more recently through the use of bioinformatics. Semiconductor manufacturers such as Intel have designed BIGstack solutions for the automated processing of genomic data, using advances in Intel CPU designs, and is providing NVMe solutions, and more advanced RSD designs. The improvements in large-scale data processing capabilities and the potential scalability of these hardware solutions are expected to provide new opportunities for developing personalized treatments based on genomic data while at the same time reducing cost.

Currently, genomics research focuses on predicting the efficacy of NAC by detecting the correlation between tumor tissue gene expression and NAC efficacy. By detecting the gene expression of needle puncture tissue samples in patients before NAC, the expression of multiple genes including ER, PgR, pS2, HER2 / neu, BRCA-1, Bcl-2, P53, P21, Ki-67, and TopoII, can be correlated to the efficacy of NAC [22-28]. Two companies, Oncotype DX and Mamma Print have constructed a multi-gene expression profile for predicting the efficacy of NAC. These companies have already obtained FDA certification and their protocols are currently being evaluated in clinical trial studies [29]. However, current genomics methods may lack accuracy, therefore effects from NAC treatment are still largely under determined. Moreover, multi-gene expression profiling is only based on relatively small sample sizes and is still at its infancy as the interrelations between gene expression and protein form and function are multi-parametric. Furthermore, due to differences in ethnic groups, the population gene expression profiles often vary widely, and there are still relatively few studies that would enable meaningful statistically significant conclusions to be drawn when addressing questions associated with the proliferation of a particular cancerous tissue molecular sub-type.

In addition to the above, a further problem encountered in clinical practice is that due to the poor specificity and low sensitivity of serum tumor markers and molecular biomarkers, diagnosis can be compromised. As a result, tumor cells in the peripheral blood of patients with

early breast cancer cannot be adequately screened on time. Although, exosomes extracted by liquid biopsy are rapidly becoming more widely used in early detection and screening, the method has not been yet routinely adopted to study tumor dynamics or the risk of recurrence, though there is significant potential in such approach as it offers advantages in terms of its low-cost and non-invasiveness.

Liquid biopsies rely on screening the peripheral blood by collecting circulating tumor cells (CTCs), and/or circulating tumor DNA and RNA (ctDNA/RNA) [30]. Exosomes are secreted by all living cells and contain the genetic information of their cells of origin. Once released, their content provide a snapshot of the information of their parent cells, furthermore, they remain sufficiently stable for a sufficiently long time so their content can be sampled as they move within the circulatory system. It is now well accepted that exosomes and their contents play key roles in the development of breast cancer, including promoting tumorigenesis, metastasis, angiogenesis, immune escape, and treatment resistance [31]. This unique property makes exosomes the most significant new type of marker for early diagnosis, prognosis monitoring, and treatment of breast cancer. Wang et al. reviewed their roles and discussed their potential use in clinical applications for breast cancer screening [31].

D. Combining genomics and radiomics for the prediction of NAC efficacy

The goal of radiomics is to integrate information from medical images, with high-fidelity transcriptomics, proteomics and metabolomics high-throughput data. Data mining techniques is used to extract features from the imaging process and phenotypic, which is correlated to extracted genotypic information and protein characteristics, in order to build descriptive models of predictive value.

Baumann et al. 2003 [32] introduced a radiomics protocol named GEENEPI (genetic pathways for the European Society of Radiotherapy and Oncology) to predict the efficacy of radiation treatment of tumours. Radiogenomics has the potential to explore the sensitivity associated with peritumoral normal tissue as opposed to tumour tissue when these are irradiated through a treatment protocol.

Radiogenomics inherits the advantages of non-invasive, real-time and reproducible imaging, using computer tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) and other medical imaging modalities to obtain global information about disease proliferation in several spatio-temporal scales and levels of resolution [8]. At the same time, it also inherits the advantages of genomics that incorporate high throughput analysis at the molecular level. Its major advantage over gene on a chip type analysis is that the latter only reflects the gene expression level at the sampling site at a certain point in time (that is, during biopsy/resection of the tumor). Furthermore, radiogenomics reflects gene expression level associated with the entire tumor tissue with further localization identified through the tumorous tissue imaging process.

Chemotherapy is one of the most well established modalities for treating advanced breast cancer. Neoadjuvant chemotherapy (NAC) is a safe and effective approach in the treatment of locally

advanced and inoperable breast cancer that may be administered before surgery [33]. Its main goal is to decrease tumor size [34]. By decreasing tumor size, NAC may enable patients, who would otherwise undergo mastectomy, to be treated with breast-conserving therapies. Unfortunately, not all breast cancer patients are suitable for NAC treatment, and under normal circumstances, pathologic complete remission (pCR) that is achieved following NAC appears to vary widely according to tissue molecular subtypes [35] and can show significant variation among patients [33]. A significant proportion of patients are insensitive to NAC, and some experience tumor progression even during NAC treatment. Therefore, it is extremely important for clinicians to be able to make an early decision whether or not a tumor responds to NAC.

III. Results

A. Progress on analytical methods of radiogenomics

1. Progress on analytical methods for genomic datasets

Genomics data analysis allows understanding the key factors that affect disease proliferation at the molecular level by linking them to specific metabolic pathways, and thus providing additional understanding of the mechanism of disease progression, so that alternative treatment protocols may be considered. Gene expression profiling aims at obtaining a list of significant gene expression changes between pathological or healthy tissue through differential gene expression analysis. The obtained gene list can be used as a genomic data feature vector alone for subsequent fusion analysis, or the gene list can be analyzed after further analysis of the resulting proteome and its effect on the metabolome. To analyze the pathways of differential gene expression, Gene Ontology (GO) term enrichment analysis [36] or Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis methods [37] can be used to obtain network information of these genes such as their interference to biochemical reactions and physiological functions. Weighted gene co-expression network analysis (WGCNA) is an algorithm for mining module (mode) information from high-throughput data, which can mine gene expression profile data with the same or similar expression trends of gene modules and is currently showing significant potential in bridging the gap between our understanding of genome-metabolome interrelationships [38].

As a data-driven science, genomics largely utilizes machine learning to capture dependencies in data and derive novel biological hypotheses [39]. Machine learning methods can usefully be segregated into two primary categories: supervised versus unsupervised methods [40]. A supervised learning algorithm for gene finding requires an input as a training set of labeled DNA sequences, where the labels specify the locations of the start and end of the gene (TSS and TTS) as well as all of the splice sites in between. Then this training data is used to identify general motifs in gene expression, such as what DNA sequence pattern typically occurs near a donor or acceptor splice site. The goal of such a classification model is to identify novel genes that resemble the genes in the training set according to the identified motifs [40].

Support vector machine (SVM) when used in its simplest form as a supervised machine learning method is a powerful classification tool for cancer genomic classification or subtyping. The resultant classification may be correlated with disease outcome prognosis, drug efficacy prediction, and may be used to elucidate tumorigenesis drivers, or other tumor-specific biological

processes. Placing SVM in a wider Artificial Intelligence context can lead to identification of new patterns associated with disease assessment and rate of proliferation [41].

Unsupervised learning, such as clustering and principal component analysis, uses machine learning algorithms to analyze and cluster unlabeled datasets, the goal of which is to learn inherent patterns within the data themselves. An unsupervised machine learning method was suggested by Lopez et al. [42] where clusters of patients based on their genomic similarity were identified, the study also accounted for family-wise-error rate, as a result of identifying clusters from the underlying structure of the data and not just due to random mutation. Their approach takes advantage of the high degree of linkage disequilibrium between Single Nucleotide Polymorphisms (SNP) by pruning correlated nearby SNPs, thus helping reduce redundant variants in the dataset. A gene pathway analysis for the potential relationships between the clusters can therefore be developed as illustrated in Figure 1.

Large neural networks are a class of machine learning algorithms that can simultaneously make predictions, and perform dimensionality reduction. Compared to traditional machine learning algorithms used in genomics, deep learning using neural networks has a larger model learning capacity and higher flexibility than traditional machine learning algorithms. A classical deep learning algorithm may have millions of parameters to be trained. The flexibility of deep learning allows it to automatically learn features and patterns through proper cluster training without manual segmentation and labeling. At the same time, the flexibility of these algorithms leads to a lack of interpretability of the resultant models. Consequently, deep learning needs to be applied with caution when it is used for automatic diagnosis of disease proliferation.

As with all other machine learning methods, successful application of deep learning also requires domain knowledge. Selection of the most appropriate deep learning methodology for biological sequence analysis, is not straightforward, as the adopted method may directly bias the results. In deep learning, domain knowledge is built into the design of the network architecture. Such information can then be used to figure-out which layers can be adaptive. Choices on network architecture are also important as they determine the degree of learning of the network. Adaptive methods may also be used to determine the generalization ability of the network.

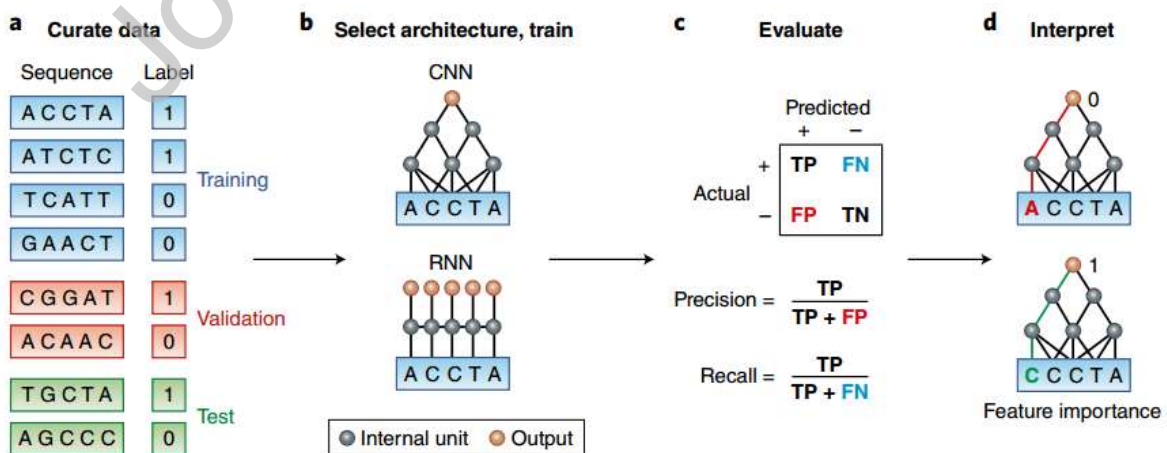


Figure 1 Deep learning workflow in genomics. a) A dataset should be randomly split into training, validation and test sets. The positive and negative examples should be balanced for potential confounders (for example, sequence content and location) so that the predictor learns salient features rather than confounders. b) The appropriate architecture is selected and trained on the basis of domain knowledge. For example, CNNs capture translation invariance, and RNNs capture more flexible spatial interactions. c) True positive (TP), false positive (FP), false negative (FN) and true negative (TN) rates are evaluated. When there are more negative than positive examples, precision and recall are often considered. d) The learned model is interpreted by computing how changing each nucleotide in the input affects the prediction. The four steps of this workflow are discussed in further detail in [42].

2 Progress on analytical methods of medical image data

Realizing precision medicine requires precise genotypic and phenotypic identification. High-throughput genomic data provides accurate genotypes, whereas medical imaging data is an important source of accurate phenotypic expression. Analyzing images therefore could also lead to better understanding of disease-related phenotypic expression to further refine current understanding of new image features that can be extracted for disease diagnosis [40].

2.1 Traditional computer vision for tumour segmentation via MR image

Segmenting images into regions of interest such as tumors, normal tissues and other anatomical structures is the most critical part in medical image analysis. Many tumors have unclear boundaries, therefore, it is necessary to develop automated medical image segmentation algorithms. Commonly used segmentation algorithms include a region growth method, a level set method [43], an image cluster/reconstruction method [44], morphological algorithms, active contour (snake) algorithms and semi-automatic segmentation methods (live-wires), etc. [45].

Considering these single segmentation methods have their own limitations, so generally, two or more traditional methods are often combined to complement each other for a better segmentation result. For example, one can employ an interactive segmentation based on the active contour without edges algorithm using parallel programming routines with graphics processing units, as such a method is numerically intensive [46]. Meanwhile, such a method can be designed or used based on Fuzzy C-Mean Clustering and Fuzzy SVM Algorithm [47], or a semi-supervised

method based on texture features and mean intensity levels, combined with advanced clustering techniques [48]. Some of these traditional methods generally require morphological operations such as erosion and expansion, for post-processing to obtain a relatively smooth tumor border.

2.2 Deep learning based tumour segmentation techniques

Modern image segmentation techniques can be enhanced by deep learning algorithms. Examples of deep learning methods include the tumour detection methods based on multi-layer neural networks and active contour models [49], as well as breast tumour segmentation via MRI based on deep neural networks and random forest algorithms [50]. Several deep learning-based computer-aided detection (CAD) systems have been developed for tumor detection and segmentation. Since the first object detection systems using convolution neural networks (CNNs) were proposed in 1995, breast tumor segmentation using deep learning has been applied in many medical imaging applications [51-54]. The authors in [53] used a segmentation approach based on the U-Net architecture. The proposed technique has been validated on a dataset of 66 breast T1-MR breast images. By combining SegNet and U-Net, Zhu et al. created two CNN architectures for the detection and segmentation of 131 breast DCE-MRI images, an advantage of these segmentation routines was that they could even be used with relatively small datasets [54].

A combination of tumor detection and segmentation tasks has been explored by Jiao et al. [55] by designing two deep learning frameworks that operate simultaneously. Deep convolutional neural networks (DCNN) were employed for breast segmentation and a faster region growth with convolutional neural network was used for mass detection on segmented breast tissue images. The model was validated on a relatively large dataset of DCE-MRIs from 75 patients. The average sensitivity for mass detection achieved was 0.874 with 3.4 false positives per case. However, this deep learning model required a lot of additional support by the user as it operated via marked tumour images, the quality of which relied heavily on data annotation done manually or semi-automatically. As the slight differences between breast cancer tumor areas and background, the small breast tumor areas were too difficult to identify for direct segmentation.

Redmon et al. [56] put forward a new idea for breast tumour detection and segmentation. Because breast tumor data is not very complex for a single detection task, they used You-Only-Look-Once v2 (YOLOv2) software which is known for its good fit and speed, to perform rough inspections in order to locate tumors in a full mammogram. A drawback of the method is that because the breast tissue dataset set can be small, it is not realistic to perform fine segmentation based on the detection frame area. Therefore, it is necessary to select a larger block of interest according to the center of the detection frame and send it to a Full resolution Convolutional Network (FrCN) for segmenting the located tumor region. The above study is an example of using CNN networks for diagnosis, and the technique may be adopted or classifying segmented ROI as either benign or malignant.

Of relevance to the above studies, Al-antari et al. [57] proposed a CAD system consisting of three deep learning stages, involving YOLO for detecting, FrCN for segmenting and a deep convolutional neural network (DCNN) for classifying the tumors in mammographic images. YOLO detection produces a mass detection accuracy of 98.96%, the mass segmentation results

via FrCN produced an overall accuracy of 92.97%, whereas classification using CNN achieved an overall accuracy of 95.64%, respectively.

2.3 Transfer learning for medical image analysis

The main potential of CNN lies in its ability to extract a series of distinguishable features in multiple layers of abstraction. As mentioned earlier, the deep CNN model is a supervised learning model, and training CNN from scratch is a significant challenge that may be partitioned into the following three aspects. Firstly, since the recent trend in CNN algorithms are optimization for a greater level of abstraction, CNNs require an ever larger number of labeled training sample data. This can be impractical as medical expert labeling is very expensive, and in some cases (such as tumor data classified by type and tissue characteristics) are rare.

Secondly, CNN requires significant computational resources capable of efficiently handling training, and testing to optimize the deep learning models. Thirdly, training deep CNN of biomedical images is becoming more complicated as the number of features is increased and is riddled by overfitting and convergence problems. It is often the case that one needs to adjust the framework or network learning hyper-parameters with internal dependencies, such as the learning rate, kernel sizes of convolutional filters, the number of layers etc. This practice makes them particularly expensive for tuning [58]. To address this challenge, transfer learning methods may be adopted; these can make use of natural mapped images or complementary data sets from different medical fields for pre-training in a supervised manner a CNN network.

There are two typical strategies that may be used for transfer learning: The first one is to use a pre-trained network as a feature extractor. The work discussed in [59] found that although there is a very big difference between medical images and natural images in terms of imaging principles and image appearance, a CNN model trained with ImageNet can still be used in medical image recognition applications. For instance, in [60], the fully connected layers of a pre-trained CNN were replaced with a new logistic layer, and then the labeled data were used to train only the appended layer, while keeping the rest of the network the same. This treatment achieves a feature generator that together with manually identified features enables improved chest pathology identification [60] and yields promising results for the classification of unregistered multi-view mammograms [61].

As a radiomics approach in DCE-MR images, Bhooshan et al. [62] combined computer-extracted MR imaging kinetic and morphologic features, to classify a dataset containing 32 benign, 71 DCIS, and 150 IDC cases, with an AUC value of 0.83 regarding the classification performance. Finally, deep learning was tried in [54, 63], with the purpose of predicting invasive cancer after DCIS diagnosis. They used a transfer learning approach, in which a pre-trained GoogleNet was used to calculate features in 131 MRI images, then training a support vector machine (SVM) with an AUC value of 0.70.

The second strategy is to use the target medical data to fine-tune the pre-trained network. The pre-trained CNN is used as the initial value of the supervised learning network, and the task-related labeled data set with limited size is used for fine-tuning the network parameters with

supervision, adjusting several or all layers in the network [64-65]. Vianna [66] studied how to utilize transfer learning to build an X-ray image classification system, and found that a fine-tuned transfer learning system with data augmentation effectively enables to alleviate overfitting problems, so that deep fine-tuning has improved performance compared to fine-tuning at shallow layers. It is important to use fine-tuned networks when the training set size is reduced [67].

In [68], Tajbakhshba et al. emphasized that fine-tuning a pre-trained CNN in a layer-wise manner leads to incremental performance improvement, compared to the resultant classification performance by training a separate pattern classifier with the features extracted from the fully connected layers of a pre-trained CNN and then trained. The approach also differs from [68]–[70] wherein the entire pre-trained CNN underwent fine-tuning. As can be seen from the above discussion, both strategies have been widely used. The advantage of the former is that it does not need to train all deep networks, and it is convenient to insert the extracted features into the existing medical image analysis process, but which strategy is the best may not yet be determined with certainty.

2.4 Weakly supervised learning of medical images

In addition to using transfer learning, another strategy is weakly supervised learning, which effectively combines the advantages of unsupervised pre-training and supervised learning. Unlabeled data can be also utilized, and to extract the general features of images in an unsupervised manner. Then the extracted features are used as the initial value of the supervised learning network, and the classifier is trained using labeled data. For example, Kallenberg et al. uses convolutional sparse auto-encoder (CSAE) for breast density segmentation and breast risk assessment [71]. The main difference between CSAE and classic CNN is that the CSAE convolutional layer is pre-trained layer by layer in an unsupervised manner of SAE [72].

In the case where it is very expensive to obtain target annotation data, the combination of multiple instance learning (MIL) and deep learning is also a feasible alternative. For example, Xu et al. suggest the MIL framework can be used for both supervised and unsupervised feature learning, the results show that the performance of the MIL framework can even be better than extracting features manually, and the results can be as good as when implementing a fully supervised methodology [73]. It is now even speculated that labeling results of medical images not by medical experts but by computer scientists might be of sufficient quality so as to be used in lieu of trained medical personnel [74]. Albarqouni et al. even speculated that non-professional crowd-sourcing service platforms could also be used to complete the annotation work that would be used to train an AI diagnostic platform [75].

A current issue of concern is that deep neural networks are vulnerable to errors associated with adversarial examples. Essentially, although carefully chosen inputs are used to train the network, the network may change its output without a visible change to a human due to hidden states [76]. The rising popularity of using Generative Adversarial Networks (GANs) has thus revealed a new challenge for classification of Adversarial Images. Adversarial images are in a nutshell images

whose class category looks obvious to a human, but are associated with massive classification failures when analysed using a deep learning network.

Conditional Generative Adversarial Network (cGAN) [77] is a type of GAN that involves the conditional identification of imaged tumours via learning the statistical invariant features (texture, color etc.) of input images and enable the segmentation of the imaged tumour region. The generator network learns the mapping from the input of tumour images, to produce a segmented image. The discriminator (i.e, adversarial term) learns a loss function to identify and learn through training this mapping by comparing the ground-truth and the predicted output. Finally, an optimized loss function combines a conventional binary cross-entropy loss with an adversarial term to encourage the generator, in order to produce an output that cannot be distinguished from the ground-truth ones [78,79].

Singh et al [77] was first to use the cGAN method to segment a breast tumor within a region of interest (ROI) in a mammogram. The generative network learned to recognize the tumor area and to create the binary mask that outlined it. In turn, the adversarial network learned to distinguish between real (ground truth) and synthetic segmentations, thus enforcing the generative network to create binary masks as realistic as possible. The cGAN works well even when the number of training samples are limited. In their work, a multi-class CNN architecture is implemented to predict the four breast tumor shapes (*i.e.*, irregular, lobular, oval and round) using the binary mask segmented via cGAN output, as illustrated in Figure 2.

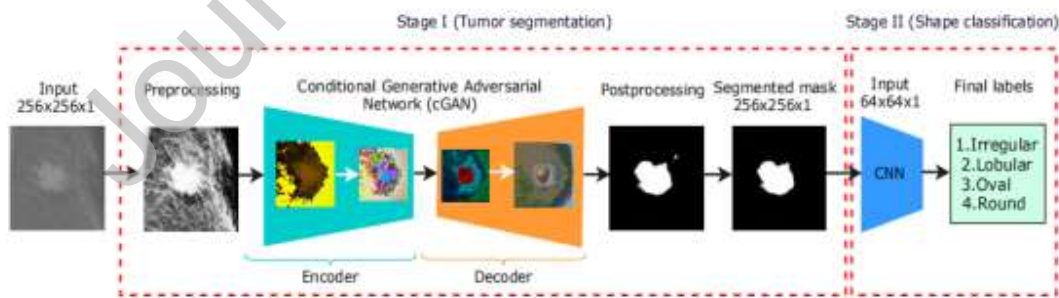


Figure 2: General framework of breast tumor segmentation and shape classification [77]. Stage 1: the tumor area has learned to distinguish between real (ground truth) and synthetic segmentations. The goal is to achieve binary mask via cGAN network with preprocessing and postprocessing to be involved. Stage II: multi-class CNN architecture is implemented to predict the four breast tumor shapes (*i.e.*, irregular, lobular, oval and round) using the binary mask segmented via cGAN output.

B. Fusion analysis between genomic data and imaging data

Once features from the two types of data (genomic/transcriptomic and imaging) are identified, it is necessary to further combine these features. Statistical-based genetic variation and image association analysis, including univariate and multivariate fusion analysis may be performed. The univariate fusion analysis only considers the degree of association between a single nucleotide polymorphisms (SNPs) locus and a specific image phenotype, using simple tests such as the Pearson chi-square test. Testing and linear regression are used in the fusion analysis of qualitative phenotype and genetic data. For example, Gauderman et al. [80] introduced a principal components (PC) regression framework to assess whether a candidate region, represented by multiple single nucleotide polymorphisms, is associated with disease.

Li et al [81] investigated the ability of computer-extracted breast MR imaging phenotypes to detect or predict the risk of breast cancer recurrence using clinically available multigene assays (MammaPrint, OncotypeDX, PAM50/Prosigna). Multiple linear regression analyses indicated that several imaging phenotypes were individually associated with recurrence scores; tumors with a high risk of recurrence were shown to be larger with more heterogeneous enhancement. Figure 3 shows a correlation heat map based on univariate linear regression analysis between each individual MR imaging phenotype and the MammaPrint, OncotypeDX, PAM50 ROR-S, and PAM50 ROR-P recurrence scores. Some imaging phenotypes correlated across the risk estimate models, whereas others did not.

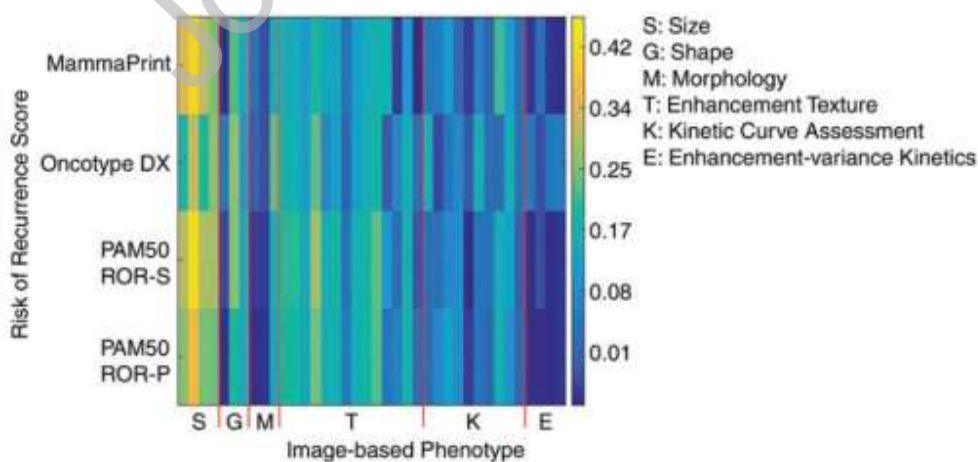


Figure 3. Correlation heat map based on univariate linear regression analysis between each individual MR imaging phenotype and the recurrence predictor models of MammoPrint, Oncotype DX, PAM50 ROR-S, and PAM50 ROR-P. In this color scale, yellow indicates higher correlation compared with blue, and the different gene assays served as the reference standard in this study. Some phenotype correlations (i.e. depicted with similar color on the above color scale) cross the risk estimate models, while others did not. [81]

A 2012 study by Yamamoto et al [2, 82] was pivotal in setting the stage for radiogenomics in breast cancer, which analyzes the correlation between quantitative image features and RNA motifs, thus showcasing the potential of this approach for the early diagnosis of non-invasive tumors. Their research results show that imaging features have significant prognostic value and can be correlated to gene expression patterns. As a result, it is possible to establish radiogenomics tags by fusing imaging, genetic and pathological features, revealing the prognostic connection between imaging and patients.

Evaluating the effect of disease treatment is also an important clinical application of radiogenomics. Malignant tumors are highly heterogeneous. It is not uncommon that cancers with the same histological type, pathological stage, and molecular type may not necessarily have the same response to radiotherapy and chemotherapy. There is currently no recognized clinical index that can effectively predict the efficacy of cancer radiotherapy and chemotherapy. Tumor phenotype and gene expression normally determine the tumors response to radiotherapy and chemotherapy. Therefore, radiogenomics methods can be used to integrate cancer clinical staging, molecular typing, and biological factors to evaluate tumor response and efficacy. Although there is still no sufficient number of studies at present, radiogenomics, as a noninvasive, quantifiable, and reproducible method, is bound to become a trend in clinical application of disease evaluation in the near future.

Figure 4 shows the overall framework of radio-genomics research and its application to medical imaging, extracting genotypic features from biomics data (including genome, transcriptomics, and epinomics, etc.). Quantitative image phenotypic features that can reflect the individual's health status can be extracted from the morphological image data (e.g., CT, MRI, PET, etc.). The association and fusion analysis of genotypic features and quantitative phenotypic features are completed through statistics or machine learning methods. The final goal is to better realize the non-invasive diagnosis, prognosis prediction and efficacy evaluation of the disease.

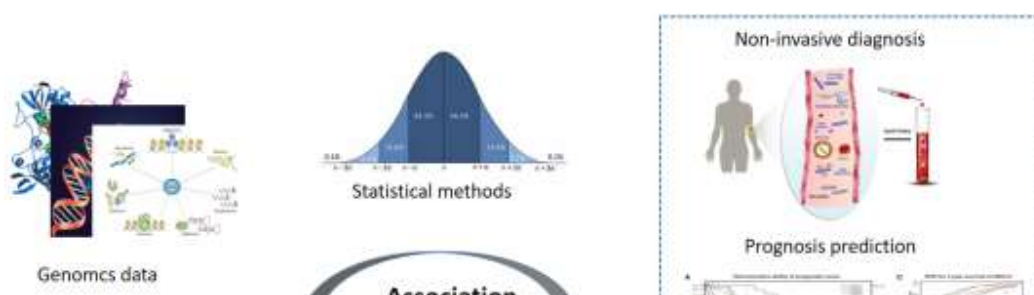


Figure 4. Schematic diagram of study and application of radiomics data fused with genomics information. The association and fusion analysis of genotypic features and quantitative phenotypic features are completed through statistics or machine learning methods. They enable the realization of the non-invasive diagnosis, prognosis prediction and efficacy evaluation of the disease.

Table 1 lists the recent researches including case studied, data modality, cohort size, methodology, along with extracted features and resultant performance. This aims at a reference for reader to differentiate between methodologies and performance, while they are aware of the types of available data.

Table 1 Recent researches in terms of case study, data modality, cohort size, methodology, along with the features and resultant performance.

Research group	Particular case	Modality	Cohort size	Method	Features	Predictive performance
D'Amico et al. [12]	Identification between benign and malignant lesions of breast	DCE-MRI Scan	12 malignant33 and benign	The k-nearest neighbour classifier based on 35	Texture Analysis (200 radiomic features were	Sensitivity:100% Specificity:90% Accuracy: 94%

	tissue		lesions.	selected features	extracted)	
Fusco et al. [13]	Differential diagnosis between benign and malignant breast lesions	DCE-MRI Scan	26 malignant and 22 benign lesions.	Decision tree; Bayesian classifier	Morphological and dynamic features of breast lesions	Accuracy: 91.7% Sensitivity:92.3%, Specificity: 90.9%
Sutton et al. [14]	Distinguishing between different invasive ductal carcinoma (IDC) subtypes	Magnetic resonance (MR) images	178 breast cancer patients	Support vector machine; Leave-one-out cross-validation (LOOCV)	Clinical pathological characteristics with extracted radiomics characteristics	Accuracy for each subtype: 89.2% (ERPR+) 63.6% (ERPR-HER2+) 82.5% (TN)
Fan et al. [20]	Identification of four molecular subtypes: luminal A, luminal B, (HER2)-over-expressing, basal-like.	DCE-MRI	60 breast cancer patients	Evolutionary algorithm for feature selection; multi-class logistic regression classifier for training datasets	90 features : 88 imaging features (morphology, texture, dynamic features) and 2 clinical information-based parameters (age and menopausal status)	The luminal A, luminal B, HER2 and basal-like subtypes are with AUC values of 0.867, 0.786, 0.888 and 0.923, respectively.
Jiang et al. 2014 [36]	Analyze the pathways of differential gene expression	Next generation sequencing (NGS) data	13 pig individuals	Gene Ontology (GO) term enrichment analysis	Read depth (RD) method in whole-genome shotgun sequence detection (WSSD)	The agreement rate, detection power and the positive prediction rate for the RD validation are 74.9%, 71.2% and 95.1%, respectively.
Ogata et al. 1999 [37]	A knowledge base for systematic analysis of gene functions, linking genomic information with higher order functional information.	GENES database; PATHWAY database;LIGAND database	29 species; and 24 completely sequenced genomes— totals ~110 000 entries,	Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis	Genome maps and manipulating expression maps, as well as gene sequence comparison, graph comparison and path computation.	N/A
Bakhtiarzadeh et al. 2018 [38]	To test whether the topology or connectivity pattern of the modules was preserved in MMES and/or MSES.	Publicly available microarray data	N/A	Weighted gene co-expression network analysis	Topology or connectivity pattern of the modules for minimal/mild endometriosis (MMES), mild/severe endometriosis	Identified sixteen co-expression modules

					(MSES)	
Lopez et al. [42]	Identify potential relationship between the clusters in the context of known biological knowledge.	Genomic dataset	191 multiple sclerosis patients	Clustering, plus statistical test, for a gene pathway analysis	High degree of linkage disequilibrium between single nucleotide polymorphisms	Average Rand index of 0.969 at an alpha level of 0.05
Yin et al. 2017 [44]	Three-dimensional voxel reconstruction from a series of temporal images	Breast DCE-MRI	7 categories of lesions to be reconstructed at 6 time frames	Tensor algebra+Principal component analysis+fuzzy C-means	Spacial and temporal associated features	Reconstructed tumours segmentation with clear and continuous boundaries; + improved voxel clustering in tumour regions of interest
Zavala-Romero et al. 2018 [46]	Segmentation for breast cancer lesions in DCE-MRI images	Breast DCE-MRI	32 breast DCE-MRI cases	Active contour without edges via parallel programming with GPU	Speedup, with comparison with non-GPU based approaches.	A high speedup (40 or more) is obtained for high resolution images, providing real-time outputs.
Chowdhary et al. 2020 [47]	Efficient segmentation system	The Mammographic Image Analysis Society (MIAS)	320 digital mammogram images	Intuitionistic possibilistic fuzzy c-mean (IPFCM) clustering	Texture, shape, margin, and intensity; mean, standard deviation, smoothness, skewness, uniformity, entropy, and kurtosis.	Average segmentation accuracy for MIAS images with different noise level 5%, 7% and 9% of IPFCM is 91.25%, 87.50% and 85.30% accordingly.
Zhu et al. 2019 [54]	Diagnosis of ductal carcinoma in situ (DCIS)	Breast DCE-MRI	131 patients with DCIS	SegNet and U-Net for transfer learning	GoogleNet model pre-trained on ImageNet as the feature extractor	Highest AUC obtained was 0.68 (95% CI: 0.57-0.77)
Jiao et al. 2020 [55]	Breast segmentation and mass detection	Breast DCE-MRI	75 patients	U-Net++; Faster region growth with convolutional neural network	Deep learning based feature learning	Dice, Jaccard coefficients, segmentation sensitivity were 0.951, 0.908, and 0.948, respectively.
Al-antari et al. 2018 [57]	Detect and segment breast mass	Mammograms-INbreast database	115 cases (410 images)	Deep model based YOLO +full resolution convolutional network	Deep learning based feature learning	Mass detection accuracy of 98.96%, Matthews correlation coefficient (MCC) of 97.62%, and F1-score of 99.24%

Ginneken et al. 2015 [60]	Nodule detection	Computed tomography LIDC data set.	865 scans; 37,262 candidate locations	Off-the-shelf CNNs; linear SVM	4096 features from the penultimate layer of OverFeat	The maximally achievable sensitivity is 78%.
Bhooshan et al. 2010 [62]	Discriminating between malignant and benign lesions; yielding MR imaging based prognostic markers	DCE-MR images	132 benign, 71 ductal carcinoma in situ (DCIS), 150 invasive ductal carcinoma (IDC) lesions	Stepwise linear discriminant analysis ; Bayesian neural networks	Morphologic and kinetic features were extracted	Classification between DCIS and IDC with AUC of 0.83 ± 0.03 (standard error). AUCs were 0.85 ± 0.02 for separation between IDC and benign lesions; and 0.79 ± 0.03 for DCIS and benign lesions
Tajbakhshba et al. 2016 [68]	Medical image classification, detection, and segmentation; investigating the performance of deep CNNs to be trained from scratch	Radiology, cardiology, and gastroenterology	40 colonoscopy videos; Training: 3,800/15,100 frames with and without polyps; Test: 5,700/13,200 frames with & without polyps	Knowledge transfer based CNN network; pre-trained deep CNNs with sufficient fine-tuning	Training with the use of 1.2 million images labeled with 1000 semantic classes.	Fine-tuning process led to a significant decrease in segmentation error ($p < .0001$); Reduced localization error is significantly lower ($p < .0001$) than that of handcrafted approach with feature of shape, color, texture; where p labels important association via statistical tests.
Kallenberg et al. 2016 [71]	Unsupervised feature learning method; Breast density segmentation & scoring of mammographic texture	Mammography: Dutch Breast Cancer Screening Dataset	Averaged posteriors of 500 patches randomly sampled from breast area	A novel sparsity regularizer is used to learn a feature hierarchy from unlabeled data.	Deep CNN features of multiscale image patches. Percent density (PMD) is computed for evaluation.	A very strong positive relationship with the manual Cumulus scores ($R=0.85$) with an AUC of 0.59
Xu et al. 2014 [73]	Weakly supervised method for colon cancer classification and to outline cancer regions	High resolution histopathology images	Histopathology images of 132 patients with obtained 9801 patches as instances in an image	Multiple instance learning (MIL)	Scale-invariant feature transform (SIFT), Local Binary Pattern (LBP), $L \times a \times b$ color histogram as manual features; last hidden layer in deep learning as fully supervised features; Single layer network of centroids from K-	Accuracy of unsupervised feature learning (93.56%), the MIL framework with coarse label (96.30%)

					means clustering as unsupervised features	
Singh et al. 2020 [77]	Segment breast tumor within a region of interest (ROI)	Digital Database for Screening Mammography (DDSM)+ INbreast dataset	106 breast tumor images from INbreast dataset; 1,168 cases of breast tumors from DDSM	Conditional Generative Adversarial Network (cGAN)	Classify generated masks into four tumor shapes: irregular, lobular, oval and round	A high Dice coefficient and Intersection over Union (IoU) of 94% and 87%, respectively, with an overall accuracy of 80%
Gauderman et al. 2007 [80]	Analyze association between respiratory symptoms in children and four SNPs in the Glutathione-S-Transferase P1 locus	Data from the Children's Health Study.	More than 12,000 school children living in southern California are involved	Principal components (PCs) analysis to compute combinations of SNPs and capture linkage-disequilibrium information	Respiratory symptoms in children and four single nucleotide polymorphism (SNPs) in the Glutathione-S-Transferase P1 locus.	Stronger evidence of an association using the PC approach ($p=0.044$) than either genotype based ($p=0.13$) or haplotype-based ($p=0.052$) approach, where p labels important association via statistical tests.
Li et al. 2016 [81]	To investigate relationships between breast MRI phenotypes with multigene assays of MammaPrint, Oncotype DX, and PAM50	MR Imaging radiomics	84 breast MRI scans, along with clinical, histopathologic, and genomic data.	Multiple linear regression and receiver operating characteristic analysis for the predictive ability of MRI radiomics	MRI radiomics feature: tumor phenotypes of size, shape, margin morphology, enhancement texture, and kinetic assessment	Significant associations ($R^2 \in [0.25, 0.32]$, $r \in [0.5, 0.56]$, $P < .0001$) between radiomics signatures and multigene assay recurrence scores
Yamamoto et al. 2012 [82]	A preliminary radiogenomic association map linking MR image phenotypes to underlying global gene expression patterns in breast cancer	Breast MRI+gene sets selected from the GSEA database	333 gene sets related to breast cancer against 10 patients with MRI	Radiogenomic analysis: Bioinformatics analysis Gene set enrichment analysis	Tumor transcriptome profiles using Affymetrix GeneChip Human Genome U133 Plus 2.0 (54675 probes); A set of binary imaging traits was defined as a priori using radiogenomic AMP assay (ImageDx)	21 imaging traits globally correlated ($p < 0.05$), with 71% of the total genes measured. 12 imaging traits significantly correlated (false discovery rate < 0.25) with gene sets of breast cancer and 11 traits correlated (false discovery rate < 0.25) to prognostic gene sets

IV. Discussion: Opportunities and challenges

As we further explore multi-dimensional analysis in relation to radiogenomics, it is important to discuss the benefits and challenges that come to light. The goal of this discussion is to share the data analytics opinions and perspectives relating to the new opportunities and challenges brought forth by MRI radiogenomics [83-86].

A. Establishment of a vectorized model for multi-scale and multi-dimensional space-time consistency analysis based on geometric algebra

DCE-MRIs have typical spatio-temporal characteristics and existing models are inadequate to effectively interpret the complex relationship of multi-layer spatio-temporal data. Therefore, it is necessary to develop spatio-temporal consistent analysis models that can analyze the temporal and spatial dimensions to better correlate the image characteristics across various dimensions.

1. Time-space unified deep learning

The analysis of breast MRIs requires a four-dimensional dynamic spatial image analysis processing platform. Developing deep learning models with un-structural output is the focus of current high-dimensional medical image processing and analysis. Based on geometric algebra, Yin et al 2017 proposed a framework for deep learning of high-dimensional medical images. By decomposing high-dimensional images into simple geometric elements such as points, lines, areas, and volumes, and combining geometric algebra to analyze the characteristics of multidimensional consistency of spatiotemporal data, a multi-dimensional, multi-scale deep learning classification system can be designed [87-89]. As discussed in [90], a scalar product can be conveniently extended to Clifford or geometric product to account for errors due to a patient's movement, to extract non-linear features from images, or to account for observed scaling changes across the dimensions of a tumour, as illustrated in Figure 5. Time domain terahertz spectroscopy and MRI which are complementary sensing modalities may be used as part of a diagnostics protocol and in that case time-space unified deep learning schemes that combines all these heterogeneous datasets needs to be adopted. This becomes feasible through the application of algorithms that use geometrid products to combine multiple features.

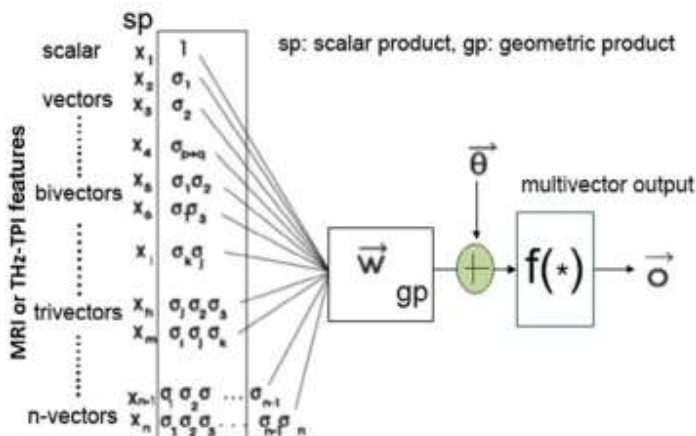


Figure 5. Geometric neuron based on the McCulloch-Pitts neuron for MRI and THz-pulse imaging datasets based on the generic framework discussed in Ref. [85]. The symbol sp denotes scalar product; $\{\sigma_i\}$, $i=1,2,\dots,n$ label orthonormal basis vectors; and gp denotes geometric product.

2. Deep learning Laplacian pyramid networks for multi-scale dense residual U-Net

There are recently developed methods exploiting lateral connections between low-level feature maps across resolutions and semantic levels, including U-Net [91] and SharpMask [92] for segmentation. In addition, recombinator networks [93] have been developed for face detection, and Stacked Hourglass networks [94] have been proposed for improved key-point estimation. Ghiasi et al. [95], discussed a Laplacian pyramid image feature representation for fully convolutional networks (FCNs) to progressively refine segmentation. Lin et al. proposed feature pyramids that are viewed as a basic component in recognition systems for detecting objects at different scales. A Feature Pyramid Network (FPN) with lateral connections has been developed for building high-level semantic feature maps at all scales and has been shown to achieve significant improvement as a generic feature extractor in several applications [96]. Such developments may be adopted to integrate image features at different spatial dimensions so as to improve the generalization ability of deep learning algorithms.

Since DCE-MRIs are composed of multi-dimensional geometric images with different structures, in order to obtain multi-dimensional deep learning in a consistent manner, the convolutional layer needs to be processed through multiple kernels according to the characteristic features of the data at different dimensions. Multi-scale dimensionality reduction e.g. through a fractal dimension can be used as a universal parameter to improve on the deep learning ability of the model. A possible way of achieving this is through the combined use of a residual network and a dense convolutional network implementing a pyramid structured multi-scale dense residual U-Net as the backbone of the network.

Implementation of the above network is possible by integrating the pyramid convolution kernel into the multi-scale dense residual block of the following structure (Figure 6), and gradually reduce the depth of the convolution kernel as the convolution layer increases. Each set of inputs is an all-scale feature, and each group of output features is associated with different scales. The proposed structure can automatically extract the features of the image at each scale, and the use of $1*1$ convolution effectively reduces the overall dimension.

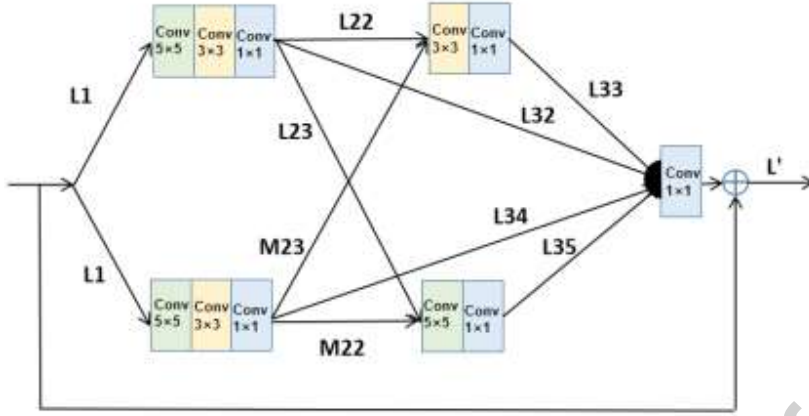


Figure 6. A pyramid structured multi-scale densely connected U-Net. The signs Conv $N \times N$ ($N=1,3,5$) represent the $N \times N$ convolutional layer at the n th layer.

The pyramid multi-scale residual block in Figure 6, is composed of three convolution kernels of different sizes (1, 3, and 5), which realize the transfer and utilization of image features between different scales through an information exchange mechanism, and at the same time redundant feature filtering are performed. The operation can be expressed as

$$L_{22} = C_{5 \times 5}^1 C_{3 \times 3}^1 C_{1 \times 1}^1 (L_1) ,$$

$$M_{22} = C_{5 \times 5}^1 C_{3 \times 3}^1 C_{1 \times 1}^1 (L_1) ,$$

$$L_{33} = C_{3 \times 3}^2 (C_{1 \times 1}^2 ([L_{21}, M_{23}])) ,$$

$$L_{35} = C_{5 \times 5}^2 (C_{1 \times 1}^2 ([M_{22}, L_{23}])) ,$$

$$L' = C_{1 \times 1}^3 ([L_{32}, L_{33}, L_{34}, L_{35}]) .$$

Where $C_{5 \times 5}^n$ represents the 5×5 convolutional layer at the n th layer, $C_{3 \times 3}^n$ represents the 3×3 convolutional layer of the n th layer, and $C_{1 \times 1}^n$ represents the 1×1 convolutional layer of the n th layer, and $[*, \dots, *]$ represents the concatenation process. At the same time, local residual learning is used to improve the information flow across image features. The output L_n of the n th

multi-scale dense residual block can be expressed as $L_n = L_{n-1} + L'$. The details of the pyramidal CNN operation are omitted here to maintain brevity but can be found in [97].

B. Intelligent diagnosis through attention based bidirectional recurrent neural networks

Currently, as the use of deep learning is relatively new in the field of radiogenomics analysis, a large number of manually labeled data is used. This is resource intensive and impractical. Many current cancer image databases are used as source databases, but the cancer image sets have many similar or related features, and the labeled data size is much larger than the target data set. Thus, many studies have adopted related knowledge cross-domain transfer learning technology to identify tumor image types. At the same time, in order to effectively combine the unstructured features of radiomics in terms of traditional breast tissue MRIs with structured vectors of genomics, and to achieve automatic and accurate prediction of the efficacy of neoadjuvant chemotherapy, we propose the use of a deep convolution learning network to perform the non-linear mapping. The feature vector output from the unstructured image based Deep Convolutional Neural Network (DCNN) can be analyzed and resampled. It is then combined with attention-based recurrent deep learning and machine learning, to design a prediction system for the efficacy of neoadjuvant chemotherapy on the basis of radiogenomics analysis. Several strategies may be adopted towards the above.

(i) A framework of generative adversarial learning

The imbalance of dimensionality of multi-dimensional image data makes the training and learning of a learning model very difficult. Each dimension of the tissue imaged has a special semantic correlation, and the image resolution in a single imaging plane is sufficiently high to provide a large amount of annotation information. Therefore, through the semantic association mapping between existing multi-dimensional data, the GAN module may be embedded between unbalanced dimensional images to generate nodes with missing dimensions, and at the same time, the semantic knowledge and labeling information of different dimensions may be subjected to the same-heterogeneous analogy transfer learning. Yin et al. discussed the use of GAN methods in the context of medical image analysis, tumour detection and classification in [98].

(ii) Attention aggregation network for the combined analysis of breast radiogenomics data

Dynamic MRI imaging of the same type of tumor imaging nodes may share some common characteristics in terms of image features, whereas characteristics associated with gene expression are usually more robust. The analysis and aggregation of the relationship between heterogeneous nodes directly determines the strength of the model's representation ability. The attention mechanism can effectively aggregate potential associated nodes, but the number of

nodes at different levels is usually large and the attributes of each node are different. Therefore, by combining the doctor's diagnostic cognitive experience with the tumor growth observed in the imaging system and the mutation mechanism in genes, different types of features may be identified. The diversified self-attention mechanism that can focus on both the local and the global scale is the key to the aggregation of nodes, and can assist in forming an effective image-gene representation model.

(a) Design of fusion mechanism of imaging genomics features incorporating an AuGRU model

The effective embedding of radiomics and genomics information is the key to establish a spatiotemporally consistent radiogenomics model. The dynamic aspect of multi-dimensional breast imaging contains also time series information, which needs to be incorporated in the deep learning model. The design of a gated loop unit with memory is therefore essential for fusing radiomics and genomics information.

The lightweight bi-directional gated recurrent unit (Bi-GRU) mode provides a two-way activation embedding method, [99] which was firstly introduced in 2014. It consists of an update gate and a reset gate. The update gate is responsible for how much the previous memory is preserved and establishes a forgetting factor parameter that is incorporated in the learning process of the network. The reset gate is responsible for combining a new input with the previous one. The Bi-GRU mode has been used by Shen et al. to extract feature information from DNA sequences. The work enabled the prediction of transcription factor binding sites with improved performance by using the extracted feature information [100]. The application of Bi-GRU networks not only improves the compatibility of variable length input DNA sequences, but also is able to capture complex context information from the input sequence, to achieve better prediction performance than other baseline methods.

Through the study of the GRU with an attentional update gate (AuGRU) model, the final goal is to achieve NAC prediction via the fusion between genomic sequence features, radiomics diagnosis, and molecular subtyping. We aim to design a bidirectional threshold recurrent neural network (BiGRU-RNN) model optimising its memory and attention mechanism, with a focus on tissue-level radiomics features input and molecular subtyping feature vectors, and integrate these with a context interaction mechanism that encodes tumor related feature vectors of genomics. This will enable the establishment of a joint representation model of radiomics and genomics data.

(b) Attention-based BiGRU-RNN analysis for NAC efficacy prediction

In order to design a deep learning network of radiogenomics for neoadjuvant chemotherapy, we propose to process simultaneously traditional breast magnetic resonance parameters and radiomics tags, and at the same time, combine the genome learned from the sequencing results after analyzing gene expression variation. Using the memory properties of the bidirectional threshold recurrent unit neural network (BiGRU-RNN), the diagnostic value of the convolution feature weight vector and the molecular subtyping-related feature vector obtained by DCNN will

be filtered through the attention mechanism. The aim is to generate an association vector with attention in the recurrent neural network. At the same time, AuGRU can calculate the similarity matrix of its genome sequence for individualized cases, thus effectively integrating and classifying medical image diagnosis features, molecular subtyping, and genomics features simultaneously. This finally results in a more accurate prediction of the efficacy of neoadjuvant chemotherapy.

A possible algorithm of attention based Bidirectional Long Short-Term Memory-Recurrent Neural Network (BiGRU-RNN) model may be composed of the following sub-routines:

I. Firstly, a resampled feature vector of radiogenomics data is processed by a deep convolutional network and the resultant parameters as the input to the attention based BiGRU-RNN mode $\{w_1...w_n\}$.

II. Secondly, after the left (GRU+) and right hidden layer (GRU-) output from the input feature weigh vectors are calculated, the hidden layer vector $\{h_1...h_n\}$ is evaluated.

III. According to the attention mechanism, calculate the output vector u_w and u_{at} related to the hidden layer vector $h_1...h_n$ and the radiomics feature vector V_{at} through the multi-layer perceptual network, $U_w = \tan(w_w h_t + b_w)$; $U_{at} = \tan(V_{at} h_t + b_w)$, and thus generate the attention weight vector $\psi = \frac{\exp(u_w^T u_{at})}{\sum \exp(u_w^T u_{at})}$

IV. The similarity matrix δ contains the similarity between the genomics vector u_g and the output attention weight vector ψ :

$$\delta(\psi, u_g) = \frac{\psi \cdot u_g}{\|\psi\| \times \|u_g\|} = \frac{\sum \psi \times u_g}{\sqrt{\sum \psi^2} \times \sqrt{\sum u_g^2}}$$

V. According to the hidden layer vector h_1, \dots, h_n and AuGRU weight vector δ , the fusion of radiogenomic feature vectors can be expressed as $s = \sum_t \delta_t h_t$

VI. The softmax function predicts the degree of the improved cancer treatment, after the patient undergoes neoadjuvant chemotherapy.

VII. Finally, resultant experiments are compared and verified with the pathological results.

The schematic diagram that summarizes the proposed attention-based BiGRU-RNN network model is shown in Figure 7.

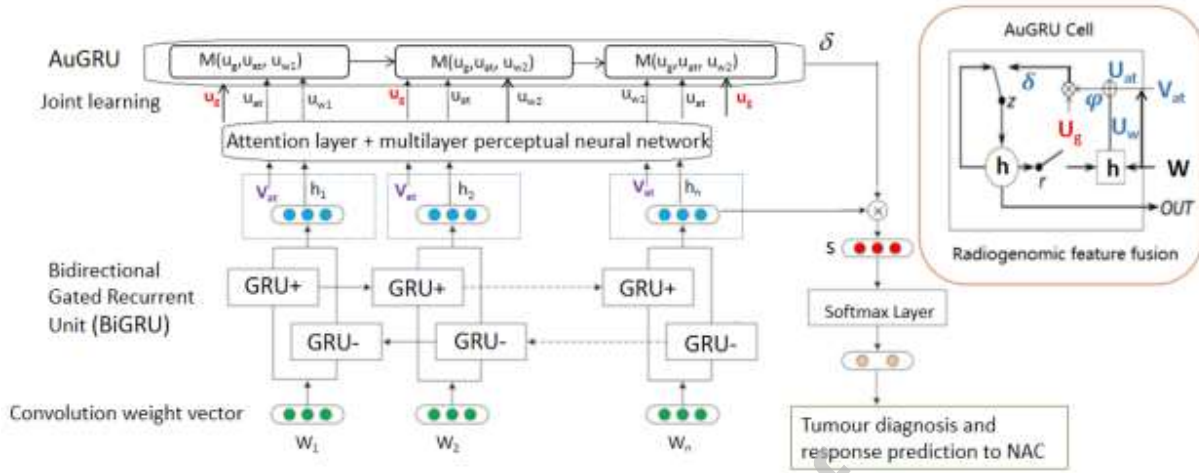


Figure 7. Schematic diagram of BiGRU-RNN network model based attention. Symbols $\{w_1, \dots, w_n\}$ are input parameters in relation to MRI radiomics, the output vectors U_w and U_{at} regard the hidden layer vector $\{h_1, \dots, h_n\}$ and the radiomics feature vector V_{at} through the multi-layer perceptron network. Similarity matrix δ contains the similarities between the genomics vector u_g and the output attention weight vector ψ : the final output of radiogenomics feature vector is achieved according to the hidden layer vector $\{h_1, \dots, h_n\}$ and AuGRU weight vector δ . Radiogenomic feature fusion is conducted as an AuGRU cell.

V. Conclusions

The association of genotypic and phenotypic features is at the core of the emergent field of Precision Medicine. It makes use of advances in biomedical big data analysis, which enables the correlation between disease-associated phenotypic characteristics, genetics polymorphism and gene activation to be revealed. Radiogenomics, a new burgeoning and interdisciplinary research field, can be used to extract characteristic motifs of gene polymorphism or gene expression from genomic datasets by integrating these with characteristic phenotypic features from different biomedical imaging modalities. Such approach makes better use of identified image features and enables the extraction of additional features from gene-image correlations that contain additional diagnostic potential. Correlations with clinical information from metabolomics may also be incorporated in the above framework. This paper principally expounded the main methods

currently adopted in the field of radiogenomics including genome data analysis, image data analysis and genome-image data fusion, with an emphasis on small size medical image analysis.

The challenging task of realizing a combined analysis of non-structural multi-dimensional medical images and structural genomics data was considered. The proposed radiogenomics analysis aims at utilizing the rich in features spatiotemporal heterogeneity of imaged cancerous tissue, while offering new exosome based genomics based diagnosis and obviating the need for invasive biopsies that can also spread cancers in the patient's body. By combining genomic information with emergent deep learning modalities, new types of correlations of diagnostic value are possible. A more focused discussion of the cGAN method to segment a breast tumor, and methods to perform fusion analysis between genomic data and imaging data from DCE-MRIs was provided. In addition, taking into consideration of recent advances in deep learning, the work proposed pyramid structured and multi-scale densely connected U-Nets and a BiGRU-RNN network model based on attention to be used for automatically evaluating treatments based on radiogenomics datasets. The discussed approaches have significant potential for predicting outcomes of the efficacy of breast cancer NAC and can potentially provide information on disease progression within a personalized medicine context.

Appendix

The following is a list of the abbreviations mentioned in this paper.

Magnetic Resonance Imaging (MRI)

Neoadjuvant chemotherapy (NAC)

Generative Adversarial Networks (GAN)

bidirectional gated recurrent unit (BiGRU)

dynamically enhanced magnetic resonance imaging (DCE-MRI)

pathological complete response (pCR)

Area under the curve (AUC)

Computer-aided diagnosis (CAD)

Diffusion weighted imaging (DWI)

Ductal carcinoma in situ (DCIS)

Gene Ontology (GO)

Kyoto Encyclopedia of Genes and Genomes (KEGG)

Weighted gene co-expression network analysis (WGCNA)

Support vector machine (SVM)

Single Nucleotide Polymorphisms (SNP)

True positive (TP)

False positive (FP)

False negative (FN)

True negative (TN)

Deep convolutional neural networks (DCNN)

You-Only-Look-Once v2 (YOLOv2)

Full resolution Convolutional Network (FrCN)

Convolutional sparse auto-encoder (CSAE)

Multiple instance learning (MIL)

Single nucleotide polymorphisms (SNPs)

Principal components (PC)

Leave-one-out cross-validation (LOOCV)

Invasive ductal carcinoma (IDC)

Next generation sequencing (NGS)

Whole-genome shotgun sequence detection (WSSD)

Intuitionistic possibilistic fuzzy c-mean (IPFCM)

The Mammographic Image Analysis Society (MIAS)

Matthews correlation coefficient (MCC)

Percent density (PMD)

Scale-invariant feature transform (SIFT)

Local Binary Pattern (LBP)

Digital Database for Screening Mammography (DDSM)

Intersection over Union (IoU)

Bi-directional gated recurrent unit (Bi-GRU)

Attentional update gate (AuGRU)

Bidirectional threshold recurrent unit neural network (BiGRU-RNN)

Declaration of Competing Interest

This is to confirm that there is no conflict for our manuscript to be submitted for publication purposes.

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Reference

- [1] Gansler T, Ganz PA, Grant M, Greene FL, Johnstone P, Mahoney M, Newman LA, Oh WK, Thomas CR, et al. Sixty years of CA: a cancer journal for clinicians. *CA Cancer J Clin*, 60(6): 345-350, 2010
- [2] Yamamoto S, Maki DD, Korn RL, Kuo MD. Radiogenomic analysis of breast cancer using MRI: a preliminary study to define the landscape. *AJR Am J Roentgenol* ;199(3):654–663, 2012
- [3] Mazurowski MA, Zhang J, Grimm LJ, Yoon SC, Silber JI. Radiogenomic analysis of breast cancer: luminal B molecular subtype is associated with enhancement dynamics at MR imaging. *Radiology* 2014; 273(2): 365-372
- [4] Metcalfe P, Liney GP, Holloway L, Walker A, Barton M, Delaney GP, Vinod S, Tome W. (2013). The potential for an enhanced role for MRI in radiation-therapy treatment planning. *Technology in cancer research & treatment*, 12(5), 429–446, 2013
- [5] Liu Z, Wang S, Dong D, Wei J, Fang C, Zhou X, Sun K, Li L, Li B, Wang M, Tian J. The Applications of Radiomics in Precision Diagnosis and Treatment of Oncology: Opportunities and Challenges. *Theranostics*, 9(5):1303-1322. 2019
- [6] Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*, 384(9938):164-72, 2014
- [7] Ye DM, Wang HT, Yu T. The Application of Radiomics in Breast MRI: A Review. *Technol Cancer Res Treat*, 19:1533033820916191, 2020

- [8] Lee SH, Park H, Ko ES. Radiomics in Breast Imaging from Techniques to Clinical Applications: A Review. *Korean J Radiol.* 21(7):779-792, 2020
- [9] XX Yin, S Hadjiloucas, Y Zhang. Pattern classification of medical images: computer aided diagnosis, Springer Science & Business Media, 2012
- [10] Song SE, Seo BK, Cho KR, Woo OH, Son GS, Kim C, Cho SB, Kwon SS, Computer-aided detection (CAD) system for breast MRI in assessment of local tumor extent, nodal status, and multifocality of invasive breast cancers: preliminary study, *Cancer Imaging*,15(1):1, 2015
- [11] Arimura, H., Soufi, M., Ninomiya, K. *et al.* Potentials of radiomics for cancer diagnosis and treatment in comparison with computer-aided diagnosis. *Radiol Phys Technol* **11**, 365–374 (2018)
- [12] D'Amico NC, Grossi E, Valbusa G, Rigioli F, Colombo B, Buscema M, Fazzini D, Ali M, Malasevski A, Cornalba G, Papa S. A machine learning approach for differentiating malignant from benign enhancing foci on breast MRI. *Eur Radiol Exp.* 4(1):5, 2020
- [13] Fusco R, Di Marzo M, Sansone C, Sansone M, Petrillo A. Breast DCE-MRI: lesion classification using dynamic and morphological features by means of a multiple classifier system. *Eur Radiol Exp.* 1(1):10, 2017.
- [14] Sutton EJ, Dashevsky BZ, Oh JH, Veeraraghavan H, Apte AP, Thakur SB, Morris EA, Deasy JO. Breast cancer molecular subtype classifier that incorporates MRI features. *J Magn Reson Imaging*, 44(1):122-129, 2016
- [15] Mazurowski MA, Zhang J, Grimm LJ, Yoon SC, Silber JI. Radiogenomic analysis of breast cancer: luminal B molecular subtype is associated with enhancement dynamics at MR imaging. *Radiology.* 273(2):365-372, 2014
- [16] Pinker K, Chin J, Melsaether AN, Morris EA, and Moy L, Precision Medicine and Radiogenomics in Breast Cancer: New Approaches toward Diagnosis and Treatment, *Radiology* 287(3), 732-747, 2018
- [17] Li, H., Zhu, Y., Burnside, E. *et al.* Quantitative MRI radiomics in the prediction of molecular classifications of breast cancer subtypes in the TCGA/TCIA data set. *npj Breast Cancer* **2**, 16012, 2016
- [18] Li Q, Dormer J, Daryani P, Chen D, Zhang Z, & Fei B. (2019). Radiomics Analysis of MRI for Predicting Molecular Subtypes of Breast Cancer in Young Women. *Proceedings of SPIE--the International Society for Optical Engineering*, 10950, 1095044.
- [19] Xie T, Wang Z, Zhao Q, Bai Q, Zhou X, Gu Y, Peng W, Wang H. Machine Learning-Based Analysis of MR Multiparametric Radiomics for the Subtype Classification of Breast Cancer. *Front Oncol.* 9:505, 2019
- [20] Fan M, Li H, Wang S, Zheng B, Zhang J, Li L. Radiomic analysis reveals DCE-MRI features for prediction of molecular subtypes of breast cancer. *PLoS One*, 12(2):e0171683, 2017
- [21] Bansal GJ, Santosh D. Accuracy of MRI for prediction of response to neo-adjuvant chemotherapy in triple negative breast cancer compared to other subtypes of breast cancer. *Indian J Radiol Imaging*, 26(4):475-481, 2016
- [22] Caudle AS, Gonzalez-Angulo AM, Hunt KK, Liu P, Pusztai L, Symmans WF, Kuerer HM, Mittendorf EA, Hortobagyi GN, and Meric-Bernstam F. Predictors of tumor progression during neoadjuvant

chemotherapy in breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 28: 1821-1828, 2010

[23] Colleoni, M., I. Minchella, G. Mazzarol, F. Nole, G. Peruzzotti, A. Rocca, G. Viale, L. Orlando, G. Ferretti, G. Curigliano, P. Veronesi, M. Intra, and A. Goldhirsch. Response to primary chemotherapy in breast cancer patients with tumors not expressing estrogen and progesterone receptors. *Annals of oncology : official journal of the European Society for Medical Oncology*, 11: 1057-1059, 2000

[24] MacGrogan, G., L. Mauriac, M. Durand, F. Bonichon, M. Trojani, I. de Mascarel, and J. M. Coindre. Primary chemotherapy in breast invasive carcinoma: predictive value of the immunohistochemical detection of hormonal receptors, p53, c-erbB-2, MiB1, pS2 and GST pi. *British journal of cancer*, 74: 1458-1465, 1996

[25] Munoz-Gonzalez, D., I. Zeichner-Gancz, M. Candelaria, M. T. Ramirez-Ugalde, M. Perez-Sanchez, G. Cervantes-Vazquez, D. Cantu-de Leon, A. Mora-Tizcareno, and J. Leonor-Ortiz. 2005. Her-2/neu expression as a predictive factor for response to anthracycline-based chemotherapy in a mexican population of locally advanced breast cancer patients. *Medical oncology* 22: 23-28

[26] Mieog, JS, van der Hage JA, van de Vijver MJ, van de Velde CJ et al. Cooperating Investigators of the Tumour response to preoperative anthracycline-based chemotherapy in operable breast cancer: the predictive role of p53 expression. *European journal of cancer* 42: 1369-1379, 2006

[27] Durbecq V, Desmed C, Paesmans M, Cardoso F, Di Leo A, Mano M, Rouas G, et al. Correlation between topoisomerase-IIalpha gene amplification and protein expression in HER-2 amplified breast cancer. *International journal of oncology* 25: 1473-1479, 2004

[28] Chevillard, S., P. Pouillart, C. Beldjord, B. Asselain, P. Beuzeboc, H. Magdelenat, and P. Vielh. Sequential assessment of multidrug resistance phenotype and measurement of S-phase fraction as predictive markers of breast cancer response to neoadjuvant chemotherapy. *Cancer* 77: 292-300, 1996

[29] Cardoso, F., L. J. van't Veer, J. Bogaerts, L. Slaets, G. Viale, S. Delaloge, J. Y. Pierga, E. Brain, S. Causeret, M. DeLorenzi, A. M. Glas, V. Goulinopoulos, T. Goulioti, S. Knox, E. Matos, B. Meulemans, P. A. Neijenhuis, U. Nitz, R. Passalacqua, P. Ravdin, I. T. Rubio, M. Saghatelyan, T. J. Smilde, C. Sotiriou, L. Stork, C. Straehle, G. Thomas, A. M. Thompson, J. M. van der Hoeven, P. Vuylsteke, R. Bernardis, K. Tryfonidis, E. Rutgers, M. Piccart, and M. Investigators. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *The New England journal of medicine* 375: 717-729, 2016

[30] Batth IS, Mitra A, Manier S, Ghobrial IM, Menter D, Kopetz S, Li S. Circulating tumor markers: harmonizing the yin and yang of CTCs and ctDNA for precision medicine. *Ann Oncol.* 28(3):468-477, 2017

[31] Wang, L., Wang, B., Wen, H., Mao, J., Ren, Y., Yang, H. Exosomes: A rising star in breast cancer (Review). *Oncology Reports* 44 (2): 407-423, 2020

[32] Baumann M, Hölscher T, Begg AC. Towards genetic prediction of radiation responses: ESTRO's GENEPI project. *Radiother Oncol.* 69:121-125, 2003

[33] Wang H, Mao X. Evaluation of the Efficacy of Neoadjuvant Chemotherapy for Breast Cancer. *Drug Des Devel Ther.* 14:2423-2433, 2020

[34] Von Minckwitz G., Untch M., Blohmer J.U., Costa S.D., Eidtmann H., Fasching P.A., Gerber B., Eiermann W., Hilfrich J., Huober J., et al. Definition and impact of pathologic complete response on prognosis

after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J. Clin. Oncol.* 30:1796–1804, 2012

[35] Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, Blohmer JU, Eiermann W, Jackesz R, Jonat W, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. *J Clin Oncol*, 24(12):1940–9949, 2006

[36] Jiang J, Wang J, Wang H, Zhang Y, Kang H, Feng X, Wang J, Yin Z, Bao W, Zhang Q, Liu JF. Global copy number analyses by next generation sequencing provide insight into pig genome variation, *BMC Genomics*.15:593, 2014

[37] Ogata H., Goto S., Sato K., Fujibuchi W., Bono H., Kanehisa M., KEGG: Kyoto Encyclopedia of Genes and Genomes, *Nucleic Acids Research*, 27(1): 29–34, 1999

[38] Bakhtiarizadeh MR, Hosseinpour B, Shahhoseini M, Korte A, Gifani P. Weighted Gene Co-expression Network Analysis of Endometriosis and Identification of Functional Modules Associated With Its Main Hallmarks. *Front Genet*, 9:453, 2018

[39] Eraslan, G., Avsec, Ž., Gagneur, J. et al. Deep learning: new computational modelling techniques for genomics. *Nat Rev Genet* 20, 389–403 (2019)

[40] Libbrecht, M., Noble, W. Machine learning applications in genetics and genomics. *Nat Rev Genet* 16, 321–332, 2015

[41] Huang S, Cai N, Pacheco PP, Narrandes S, Wang Y, Xu W. Applications of Support Vector Machine (SVM) Learning in Cancer Genomics. *Cancer Genomics Proteomics*, 15(1):41-51, 2018

[42] Lopez C, Tucker S, Salameh T, Tucker C, An unsupervised machine learning method for discovering patient clusters based on genetic signatures, *Journal of Biomedical Informatics*, 85:30-39, 2018

[43] Yin XX, Ng BWH, Yang Q, Pitman A, Ramamohanarao K, Abbott D, Anatomical landmark localization in breast dynamic contrast-enhanced MR imaging, *Medical & biological engineering & computing* 50 (1), 91-101, 2012

[44] Yin XX, Hadjiloucas S, Chen JH, Zhang Y, Wu JL, Su MY. Tensor based multichannel reconstruction for breast tumours identification from DCE-MRIs, *PloS one* 12 (3), e0172111, 2017

[45] Zewei Z, Tianyue W, Li G, Tingting W, Lu X. An interactive method based on the live wire for segmentation of the breast in mammography images. *Comput Math Methods Med.* 2014:954148, 2014

[46] Zavala-Romero, O.; Meyer-Baese, A.; Lobbes, M.B.I. Breast lesion segmentation software for DCE-MRI: An open source GPGPU based optimization. In *Proceedings of the 2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018)*, Washington, DC, USA, 4–7 April 2018; pp. 211–215

[47] Chowdhary, C.L.; Mittal, M.; P., K.; Pattanaik, P.A.; Marszalek, Z. An Efficient Segmentation and Classification System in Medical Images Using Intuitionist Possibilistic Fuzzy C-Mean Clustering and Fuzzy SVM Algorithm. *Sensors*, 20, 3903, 2020

[48] Sun, L.; He, J.; Yin, X.; Zhang, Y.; Chen, J.H.; Kron, T.; Su, M.Y. An image segmentation framework for extracting tumors from breast magnetic resonance images. *J. Innov. Opt. Health Sci.* 2018, 11, 1850014

- [49] Ghayoumi Zadeh H, Haddadnia J, Montazeri A. A Model for Diagnosing Breast Cancerous Tissue from Thermal Images Using Active Contour and Lyapunov Exponent. *Iran J Public Health*. 45(5):657-669, 2016
- [50] Yurttakal, A.H., Erbay, H., İkizceli, T. *et al.* Detection of breast cancer via deep convolution neural networks using MRI images. *Multimed Tools Appl* **79**, 15555–15573 (2020).
- [51] Conte, L.; Tafuri, B.; Portaluri, M.; Galiano, A.; Maggiulli, E.; De Nunzio, G. Breast Cancer Mass Detection in DCE–MRI Using Deep-Learning Features Followed by Discrimination of Infiltrative vs. In Situ Carcinoma through a Machine-Learning Approach. *Appl. Sci.* **10**, 6109, 2020
- [52] Dalmis, M.U.; Litjens, G.; Holland, K.; Setio, A.; Mann, R.; Karssemeijer, N.; Gubern-M´erida, A. Using deep learning to segment breast and fibroglandular tissue in MRI volumes. *Med. Phys.* **44**:533–546, 2017
- [53] Badrinarayanan, V.; Kendall, A.; Cipolla, R. SegNet: A Deep Convolutional Encoder-Decoder Architecture for Image Segmentation. *IEEE Trans. Pattern Anal. Mach. Intell.* **39**:2481–2495, 2017
- [54] Zhu, Z.; Harowicz, M.; Zhang, J.; Saha, A.; Grimm, L.J.; Hwang, E.S.; Mazurowski, M.A. Deep learning analysis of breast MRIs for prediction of occult invasive disease in ductal carcinoma in situ. *Comput. Biol. Med.* **115**, 103498, 2019
- [55] Jiao H., Jiang X., Pang Z., Lin X., Huang Y. and Li, L., Deep Convolutional Neural Networks-Based Automatic Breast Segmentation and Mass Detection in DCE-MRI, *Computational and Mathematical Methods in Medicine*, 2020:Article ID 2413706
- [56] Redmon J, Divvala S, Girshick R, Farhadi A. You only look once: Unified, real-time object detection, *in: Proceedings of the IEEE conference on computer vision and pattern recognition*, pp. 779–788, 2016
- [57] Al-antari MA, Al-masni MA, Choi MT, Han SM, Kim TS. A fully integrated computer-aided diagnosis system for digital X-ray mammograms via deep learning detection, segmentation, and classification, *International Journal of Medical Informatics*, 117:44-54, 2018
- [58] Jiuxiang Gu, Zhenhua Wang, Jason Kuen, Lianyang Ma, Amir Shahroudy, Bing Shuai, Ting Liu, Xingxing Wang, Gang Wang, Jianfei Cai, Tsuhan Chen, Recent advances in convolutional neural networks, *Pattern Recognition*, 77: 354-377, 2018
- [59] Yadav, S.S., Jadhav, S.M. Deep convolutional neural network based medical image classification for disease diagnosis. *J Big Data* **6**: 113, 2019
- [60] Ginneken, B. van; Setio, A. A. A.; Jacobs, C.; Ciompi, F.; Off-the-shelf convolutional neural network features for pulmonary nodule detection in computed tomography scans, *in 2015 IEEE 12th International Symposium on Biomedical Imaging (ISBI)*, pp. 286–289, 2015
- [61] Carneiro G, Nascimento J, Bradley A. Unregistered multiview mammogram analysis with pre-trained deep learning models, in *Medical Image Computing and Computer-Assisted Intervention MICCAI 2015*, ser. Lecture Notes in Computer Science, N. Navab, J. Hornegger, W. M. Wells, and A. F. Frangi, Eds. *Springer International Publishing*, 9351:652–660, 2015
- [62] Bhooshan N, Giger ML, Jansen, S.A.; Li, H.; Lan, L.; Newstead, G.M. Cancerous breast lesions on dynamic contrast-enhanced MR images: Computerized characterization for image-based prognostic markers. *Radiology*, 254: 680–690, 2010

- [63] Zhu Z, Harowicz M, Zhang J, Saha A, Grimm LJ; Hwang ES, Mazurowski MA. Deep learning analysis of breast MRIs for prediction of occult invasive disease in ductal carcinoma in situ. *Comput. Biol. Med.* 115, 103498, 2019
- [64] Bar Y.; Diamant I.; Wolf L.; and Greenspan H.; Deep learning with non-medical training used for chest pathology identification, in *SPIE Medical Imaging. International Society for Optics and Photonics*, 2015, pp. 94 140V–94 140V
- [65] Ginneken B. van, Setio AA, Jacobs C, and Ciompi F, “Off-the-shelf convolutional neural network features for pulmonary nodule detection in computed tomography scans,” in *2015 IEEE 12th International Symposium on Biomedical Imaging (ISBI)*, pp. 286–289, 2015
- [66] Vianna VP. Study and development of a computer-aided diagnosis system for classification of chest X-ray images using convolutional neural networks pre-trained for imagenet and data augmentation, arXiv preprint [arXiv:1806.00839](https://arxiv.org/abs/1806.00839), 2018
- [67] Soekhoe D., van der Putten P., Plaat A. On the Impact of Data Set Size in Transfer Learning Using Deep Neural Networks. In: *Boström H., Knobbe A., Soares C., Papapetrou P. (eds) Advances in Intelligent Data Analysis XV. IDA 2016*. Lecture Notes in Computer Science, vol 9897. Springer, Cham, 2016
- [68] Tajbakhsh N, Shin JYS, Gurudu R, Hurst RT, Kendall CB, Gotway MB, Gotway H. Convolutional Neural Networks for Medical Image Analysis: Full Training or Fine Tuning? *IEEE Transactions on Medical Imaging*, 35(5):1299-1312, 2016
- [69] Schlegl T, Ofner J, and Langs G. Unsupervised pre-training across image domains improves lung tissue classification, *Medical Computer Vision: Algorithms for Big Data*. Springer, pp. 82–93, 2014
- [70] Chen H, Ni D, Qin J, Li S, Yang X, Wang T, and Heng PA. Standard plane localization in fetal ultrasound via domain transferred deep neural networks, *IEEE Journal of Biomedical and Health Informatics*, 19(5): 1627–1636, 2015
- [71] Kallenberg M, Petersen K, Nielsen M, Ng AY, Diao P, Igel C, Vachon CM et al. Unsupervised Deep Learning Applied to Breast Density Segmentation and Mammographic Risk Scoring, *IEEE Transactions on Medical Imaging*, 35(5):1-1, 2016
- [72] Shin H-C, Orton M, Collins DJ, Doran S, Leach MO. Chapter 7 - Organ Detection Using Deep Learning, Editor(s): Zhou, SK. *Medical Image Recognition, Segmentation and Parsing*, Academic Press, 123-153, 2016
- [73] Xu Y, Mo T, Feng Q, Zhong P, Lai M, and Chang EI. Deep learning of feature representation with multiple instance learning for medical image analysis, 2014 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP), Florence, 2014, pp. 1626-1630, doi: 10.1109/ICASSP.2014.6853873
- [74] Aroyo L, Welty C. Truth is a lie: crowd truth and the seven myths of human annotation. *AI Magazine*, 36(1): 15–24, 2015
- [75] Albarqouni S, Baur C, Achilles F, Belagiannis V, Demirci, Navab N. AggNet: deep learning from crowds for mitosis detection in breast cancer histology images. *IEEE Transactions on Medical Imaging*, 35(5): 1313–1321, 2016

- [76] Gu J, Wang Z, Kuen J, Ma L, Shahroudy A, Shuai B, Liu T, Wang X, Wang G, Cai J, Chen T. Recent advances in convolutional neural networks. *Pattern Recognition*, 77: pp.354-377, 2018
- [77] Singh VK, Rashwan H, Romaní S, Akram F, Pandey N, et al. Breast Mass Segmentation and Shape Classification in Mammograms Using Deep Neural Networks. *Expert Systems with Applications*, 139: 112855, 2020
- [78] Yamashita R, Nishio M, Do RKG et al. Convolutional neural networks: an overview and application in radiology. *Insights Imaging* 9: 611–629, 2018.
- [79] Tavolara TE., Niazi MKK, Arole V. et al. A modular cGAN classification framework: Application to colorectal tumor detection. *Sci Rep* 9, 18969, 2019
- [80] Gauderman WJ, Murcay C, Gilliland F, Conti DV, Testing association between disease and multiple SNPs in a candidate gene. *Genet Epidemiol*, 31(5):383-395, 2007
- [81] Li H, Zhu Y, Burnside ES et al. MR Imaging radiomics signatures for predicting the risk of breast cancer recurrence as given by research versions of MammaPrint, Oncotype DX, and PAM50 gene assays. *Radiology*, 281(2):382–391, 2016
- [82] Yamamoto S, Maki DD, Korn RL, Kuo MD. Radiogenomic analysis of breast cancer using MRI: a preliminary study to define the landscape. *AJR Am J Roentgenol*, 199(3):654–663, 2012
- [83] Tahmassebi, A., Wengert, G. J., Helbich, T. H., Bago-Horvath, Z., Alaei, S., Bartsch, R. et al. Impact of machine learning with multiparametric magnetic resonance imaging of the breast for early prediction of response to neoadjuvant chemotherapy and survival outcomes in breast cancer patients. *Investigative radiology*, 54(2), 110, 2019
- [84] AM O'Flynn E, Collins D, D'Arcy J, Schmidt M, de Souza NM. Multi-parametric MRI in the early prediction of response to neo-adjuvant chemotherapy in breast cancer: value of non-modelled parameters. *European journal of radiology*. 85(4), 837-842, 2016.
- [85] Daimiel Naranjo I, Gibbs P, Reiner JS, Lo Gullo R, Sooknanan C, Thakur SB. et al. Radiomics and Machine Learning with Multiparametric Breast MRI for Improved Diagnostic Accuracy in Breast Cancer Diagnosis. *Diagnostics*, 11(6), 919, 2021.
- [86] AM O'Flynn E, Collins D, D'Arcy J, Schmidt M, de Souza NM. Multi-parametric MRI in the early prediction of response to neo-adjuvant chemotherapy in breast cancer: value of non-modelled parameters. *European journal of radiology*, 85(4), 837-842, 2016.
- [87] Yin XX, Hadjiloucas S, Zhang Y, *Pattern classification of medical images: computer aided diagnosis*, Springer International Publishing, 2017
- [88] Yin XX, Jin Y, Gao M, Hadjiloucas S. Artificial Intelligence in Breast MRI Radiogenomics: Towards Accurate Prediction of Neoadjuvant Chemotherapy Responses. *Current Medical Imaging*, DOI: 10.2174/1573405616666200825161921, 2020
- [89] Yin XX, Yin L, Hadjiloucas S. Pattern Classification Approaches for Breast Cancer Identification via MRI: State-Of-The-Art and Vision for the Future, *Applied Sciences* 10(20); 7201, 2020

- [90] Yin XX, Zhang Y, Cao J, Wu JL, Hadjiloucas S. Exploring the complementarity of THz pulse imaging and DCE-MRIs: Toward a unified multi-channel classification and a deep learning framework, *Computer methods and programs in biomedicine* 137, 87-114, 2016
- [91] Ablamowicz R, Lounesto P, and Parra JM. *Clifford Algebras with Numeric and Symbolic Computations*. Boston, MA: Birkhäuser, 1996.
- [92] Ronneberger O, Fischer P, and Brox T. U-Net: Convolutional networks for biomedical image segmentation. In MICCAI, 2015.
- [93] Pinheiro PO, Lin TY, Collobert R, Dollár P. Learning to Refine Object Segments. In: Leibe B., Matas J, Sebe N, Welling M. (eds) *Computer Vision – ECCV 2016*. Lecture Notes in Computer Science, vol 9905. Springer, Cham. 2016
- [94] Honari S, Yosinski J, Vincent P, and Pal C. Recombinator Networks: Learning Coarse-to-Fine Feature Aggregation, 2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR), Las Vegas, NV, USA, pp. 5743-5752, 2016
- [95] Newell A, Yang K, and Deng J. Stacked hourglass networks for human pose estimation. In ECCV, 2016
- [96] Ghiasi G. and Fowlkes CC. Laplacian pyramid reconstruction and refinement for semantic segmentation. In ECCV, 2016.
- [97] He K, Zhang X, Ren S, and Sun J. Spatial Pyramid Pooling in Deep Convolutional Networks for Visual Recognition, in *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 37(9), pp. 1904-1916, 2015, doi: 10.1109/TPAMI.2015.2389824.
- [98] Yin, X-X, Yin L, Sillas H. 2020. Pattern Classification Approaches for Breast Cancer Identification via MRI: State-Of-The-Art and Vision for the Future, *Appl. Sci.* 10, no. 20: 7201.
- [99] Cho K, Van Merriënboer B, Gulcehre C, Bahdanau D, Bougares F, Schwenk H, and Bengio Y. Learning phrase representations using rnn encoder-decoder for statistical machine translation, *Proceedings of the 2014 Conference on Empirical Methods in Natural Language Processing*, in Doha, Qatar, Association for Computational Linguistics, pp 1724-1734, 2014
- [100] Shen Z, Bao, W, Huang DS. Recurrent Neural Network for Predicting Transcription Factor Binding Sites. *Sci Rep* 8, 15270, 2018.