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JOHN VERY LONGNAME DOE

BSc in name of previous degree

A VERY LONG AND IMPRESSIVE THESIS TITILE WITH A FORCED LINE BREAK

SOME THOUGHTS ON THE LIFE, THE UNIVERSE, AND EVERYTHING ELSE

MASTER IN MSC PROGRAM NAME

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“You cannot teach a man anything; you can only help him discover it in himself.” (Galileo).

ABSTRACT

The identification of cancer cells is a critical task in biomedical research and clinical practice, with significant implications for disease diagnosis, treatment, and prognosis. However, current methods often rely on manual annotation and interpretation of large datasets, which can be time-consuming, labor-intensive, and prone to human error.

This thesis explores the potential application of **Large Language Models (LLMs)** to identify cancer cells from various data sources, more specifically ultrasound, mammogram and thermogram images, tomosynthesis 3D images and histopathology slides. While LLMs are typically trained on text-based data, their ability to learn patterns and relationships within language can be leveraged in conjunction with other methods to analyze images and signals associated with cancer cells and masses. The challenge lies in finding ways to integrate these different approaches effectively, and to develop novel methods that can take advantage of the unique strengths of each technique. By exploring the potential applications of LLMs in image analysis, we may uncover new insights into the possibilities for combining language-based and visual-based approaches to solve complex problems in biomedical research.

The proposed research is interesting and challenging because it pushes the boundaries of what is possible using LLMs. By investigating the feasibility of applying LLMs to this problem, we aim to contribute to a deeper understanding of the potential applications of language models in biomedical research. This thesis can bring new insights into the strengths and limitations of LLMs for breast cancer identification and has the potential to contribute to the development of novel diagnostic tools and approaches.

Keywords: Breast Cancer, Large Language Models, Deep Learning, Artificial Inteligence.

RESUMO

A identificação de células cancerígenas é uma tarefa crítica na investigação biomédica e na prática clínica, com implicações significativas no diagnóstico, tratamento e prognóstico da doença. No entanto, os métodos actuais baseiam-se frequentemente na anotação e interpretação manual de grandes conjuntos de dados, o que pode ser moroso, trabalhoso e propenso a erros humanos.

Esta tese explora a potencial aplicação de modelos de linguagem de grande dimensão (LLM) para identificar células cancerígenas a partir de várias fontes de dados, mais especificamente imagens de ultra-sons, mamografias e termogramas, imagens 3D de tomossíntese e lâminas histopatológicas. Embora os LLMs sejam normalmente treinados em dados baseados em texto, a sua capacidade de aprender padrões e relações dentro da linguagem pode ser aproveitada em conjunto com outros métodos para analisar imagens e sinais associados a células e massas cancerígenas. O desafio reside em encontrar formas de integrar eficazmente estas diferentes abordagens e desenvolver novos métodos que possam tirar partido dos pontos fortes únicos de cada técnica. Ao explorar as potenciais aplicações de LLMs na análise de imagens, podemos descobrir novas perspectivas sobre as possibilidades de combinar abordagens baseadas na linguagem e visuais para resolver problemas complexos na investigação biomédica.

A investigação proposta é interessante e desafiadora porque ultrapassa os limites do que é possível fazer com LLMs. Ao investigar a viabilidade da aplicação de LLMs a este problema, pretendemos contribuir para uma compreensão mais profunda das potenciais aplicações de modelos de linguagem na investigação biomédica. Esta tese pode trazer novos conhecimentos sobre os pontos fortes e as limitações dos LLMs para a identificação do cancro da mama e tem o potencial de contribuir para o desenvolvimento de novas ferramentas e abordagens de diagnóstico.

(Traduzido com a versão gratuita do tradutor - DeepL.com)

Palavras chave: Cancro da mama, *Large Language Models*, *Deep Learning*, Inteligência Artificial.

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GLOSSARY

Virtual Staining Virtual staining is a digital simulation of traditional staining techniques, using algorithms to mimic chemical reactions and reveal specific cellular features. This technology enables pathologists to analyze tissues at multiple scales, enhancing diagnostic accuracy and reducing manual labor and costs.

YOLO YOLO stands for "You Only Look Once", a real-time object detection algorithm that detects objects in an image or video by applying a single neural network pass, making it fast and efficient. It is commonly used for tasks such as detecting pedestrians, cars, and other objects in images or videos. In the context of mammography, YOLO can be used to detect masses or tumors in breast images.

Generative Adversarial Networks (GANs) A type of deep learning model that consists of two neural networks: the Generator creates synthetic data and the Discriminator evaluates its authenticity. Through an adversarial process, they improve each other's performance, producing realistic synthetic images. This can be applied in mammography to generate training data.

Deep Generalized Canonical Correlation Analysis (Dg-CCA) A deep learning technique that aims to maximize the correlation between features from multiple sources, such as images and clinical data. By doing so, it enables the extraction of high-dimensional features that are most relevant for diagnosis, thus enhancing diagnostic precision in mammography.

Disentangled Variational Autoencoder (D-VAE) A type of deep learning model that enables the disentanglement of complex features in medical images into meaningful, independent factors. This allows for the extraction of relevant information from images and the generation of synthetic data that preserves the underlying structure of the original data, improving the performance of downstream tasks such as classification in mammography.

Area Under the Curve (AUC)	A measure of the accuracy of a model's predictions. It represents the probability that the model will correctly rank a randomly chosen positive instance (e.g. malignant tumor) higher than a negative instance (e.g. benign tumor). A higher AUC value indicates better performance, with 1 being perfect and 0.5 being no better than chance.
VGG16	A type of convolutional neural network (CNN) architecture designed for image classification tasks. It was introduced in the ImageNet Large Scale Visual Recognition Challenge 2014 and has since been widely used as a pre-trained model for various applications, including mammography analysis. The "16" in VGG16 refers to its depth, with 16 layers of convolutional and pooling operations followed by fully connected layers.
DarkNet-53	A deep CNN architecture that has been widely used for object detection tasks in computer vision applications, including those involving ultrasound images. It consists of 53 layers, with a series of convolutional and downsampling operations followed by a global average pooling layer to extract features from the input data.
CBIS-DDSM	Stands for Curated Breast Imaging Subset of Digital Database for Screening Mammography. It is a large dataset of ultrasound images collected from various sources, specifically designed to support the development and evaluation of computer-aided detection (CAD) systems for breast cancer diagnosis. The CBIS-DDSM dataset contains annotated images with labels indicating the presence or absence of masses, calcifications, and other abnormalities, making it a valuable resource for researchers working on deep learning-based image analysis techniques.

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ACRONYMS

LLM	Large Language Model
UI	User Interface
DBT	Digital Breast Tomosynthesis
CNNs	Convolutional Neural Networks
YOLO	You Only Look Once
GANs	Generative Adversarial Networks
MAP	Mean Average Precision
RNNs	Recurrent Neural Networks
ABUS	Automated Breast Ultrasound
GCNs	Graph Convolutional Networks
MINAS	Multiobjective Immune Neural Architecture Search
ERE	Evidential Reasoning based on Entropy
BO	Bayesian Optimization
SAcPS	Simulated Annealing controlled Position Shuffling
CAD	Computer-Aided Diagnostic
MLP	Multilayer Perceptron
CBAM	Block Attention Module
SE	Squeeze-and-Excitation
ViT	Vision Transformers
PHI	Protected Health Information

SYMBOLS

1

INTRODUCTION

The accurate identification of cancer cells is a critical task in biomedical research and clinical practice, with significant implications for disease diagnosis, treatment, and prognosis. The exponential growth of medical imaging technologies has led to an overwhelming volume of image data, which must be analyzed and interpreted by clinicians and researchers. However, current methods for analyzing these images often rely on manual annotation and interpretation, a time-consuming process that is prone to human error [1].

The limitations of traditional image analysis methods have been compounded by the increasing demand for precision medicine and personalized healthcare. The development of targeted therapies and immunotherapies requires a deep understanding of individual patient biology, which can only be achieved through detailed analysis of large-scale imaging data. However, the manual annotation of these images is often a significant bottleneck in research and clinical settings.

Researchers have been exploring various solutions to overcome the challenges of image analysis, including the development of novel algorithms and techniques that leverage advances in machine learning and computer vision. However, more work is needed to develop practical and effective methods for analyzing complex imaging data. This thesis aims to contribute to this effort by investigating the potential application of **Large Language Models (LLMs)** in analyzing images of cancer cells and masses [1] [2].

1.1 The problems

The process of identifying cancer cells from medical images is a complex and time-consuming task, often requiring extensive expertise and specialized knowledge. Clinicians and researchers are faced with the daunting challenge of analyzing vast amounts of imaging data, which can be overwhelming even for experienced professionals. The consequences of inaccurate or delayed diagnoses can be severe, highlighting the need for more effective and efficient image analysis methods [3].

One of the primary limitations of current image analysis approaches is their rigid structure and reliance on standardized protocols. While these methods have been refined over time, they can struggle to adapt to emerging trends and technologies in medical imaging. The increasing availability of high-resolution images and advanced imaging modalities has created a need for more flexible and dynamic analysis techniques that can accommodate the diverse range of data being generated [4].

The potential integration of LLMs into image analysis presents both opportunities and challenges. On one hand, these models have been successfully applied to a wide range of natural language tasks and may offer new insights into visual data representation. However, their adaptation to image analysis requires significant modifications to address the unique characteristics of visual information. For instance, language-based models must be able to interpret complex spatial relationships and patterns within images, which can be difficult to articulate in textual form [5].

Furthermore, the implementation of language-based models in medical imaging raises important questions about bias, accuracy, and transparency. It is essential that these models are designed with careful consideration of the potential pitfalls associated with their use, such as perpetuating existing biases or introducing new ones through their training processes. Additionally, the need for clear and interpretable results cannot be overstated, particularly in high-stakes medical decision-making environments [6].

1.2 Proposed Solution

To address the challenges of image analysis in cancer cell identification, we propose a multi-modal approach that leverages the strengths of various Large Language Models (LLMs) to analyze different types of medical images. Specifically, we will utilize a combination of publicly available LLMs trained on natural language processing tasks to extract relevant features from mammograms, ultrasounds, thermograms, tomosynthesis images, and histopathology slides. To facilitate the integration of these models with visual data, we will convert the image pixels into base64-encoded strings, enabling the LLMs to process and analyze the images in a textual format [7].

We will utilize a combination of pre-trained LLMs and adapt them to our specific task by fine-tuning them on publicly available medical imaging datasets [8] [9]. This approach allows us to leverage the strengths of each LLM architecture while also ensuring that they are optimized for our particular application.

Then, to evaluate the effectiveness of our proposed solution, we will conduct an extensive analysis of the models' accuracy, precision, recall, and F1-score on various image types. We will also investigate the impact of different hyperparameters, such as learning rates and batch sizes, on model performance and select the most suitable settings for each LLM architecture.

Our proposed multi-modal approach using LLMs offers a promising framework for analyzing medical images and identifying cancer cells. By leveraging the strengths of multiple models, we can develop a more robust and reliable system that improves upon existing methods. While our study focuses on comparing the performance of several different LLM architectures, it also highlights the need for further research into this area. Future work could involve exploring other LLM architectures or developing more sophisticated methods for combining multiple models to improve overall performance [6].

1.3 Context and Motivation

Traditional machine learning and deep learning methods have been widely used for medical image analysis, but they often require extensive technical expertise to implement and interpret. In contrast, LLMs offer a more accessible and user-friendly approach that can be easily integrated into existing clinical workflows. By representing images as text using base64 encoding through a front-end UI, we can leverage the strengths of LLMs in processing sequential data, while also making it easier for clinicians to interact with the system.

The ease of use is particularly important in medical image analysis, where doctors and clinicians may not have extensive technical knowledge or experience with machine learning algorithms. With traditional deep learning methods, clinicians often require significant training and support to accurately interpret results and fine-tune models to their specific needs. In contrast, LLMs can be easily fine-tuned using a user-friendly interface, allowing clinicians to quickly adapt the system to their workflow without requiring extensive technical expertise [10].

Furthermore, LLMs are pre-trained on vast amounts of natural language data, allowing them to learn complex patterns and relationships that may not be apparent through traditional feature engineering. This means that clinicians can focus on interpreting results rather than spending hours fine-tuning models or hand-crafting features [11].

By making medical image analysis more accessible and user-friendly, we can empower clinicians to make more accurate diagnoses and improve patient outcomes.

1.4 Document Structure

The current chapter 1 is an introductory text to contextualize the reader and present the currrent challenges at hand, as well as the brief solution to implement our work.

On chapter 2 we will present the research made by other researchers in this regard, as well as the state-of-the-art technologies that are currently used regarding this subject.

Next, on chapter 3 we will dive a bit deeper in the technical details of the implementation of our system while also presenting a work schedule and the work that is alrready beign developed.

Finally, on chapter 4 we will analyze our results and take our conclusions from it, deciding on the acccurracy (mostly) of the different models in all the situations considered durring the study.

2

State of the art

Image analysis has long been an area of active research in the field of medical examination, more specifically breast cancer detection. In recent years, the use of AI techniques has revolutionized the field, enabling the development of highly accurate models for tasks such as tumor segmentation, lesion detection, and image classification.

However, despite these advances, there is still much work to be done in developing robust and reliable medical image analysis systems that can be widely adopted in clinical settings. This chapter provides an overview of the current state of the art in medical image analysis, highlighting recent advances and challenges in areas such as deep learning architectures, data augmentation techniques, and model interpretability.

2.1 Conventional exam methods

The detection of breast cancer relies heavily on a combination of conventional examination techniques, including mammography, ultrasound, digital breast tomosynthesis (DBT), and thermography. While these modalities have revolutionized the field of breast imaging, they all share one common limitation: the reliance on human interpretation [12]. Each modality requires specialized training and expertise to accurately interpret results, which can lead to variability in diagnosis and treatment recommendations between healthcare providers. Furthermore, even with the aid of advanced technology, these methods are inherently limited by their inability to provide a comprehensive view of the breast tissue, leaving some cancers undetected or misdiagnosed.

This chapter explores the conventional examination methods currently used in clinical practice, highlighting both their strengths and limitations.

2.1.1 Mammography

Mammography has been the primary screening tool for breast cancer since its introduction in the 1960s [13]. It involves the use of low-energy X-rays to produce images of the breast tissue. The technique is based on the principle that dense breast tissue absorbs more

X-ray energy than fatty tissue, resulting in a higher contrast between normal and pathological tissues.

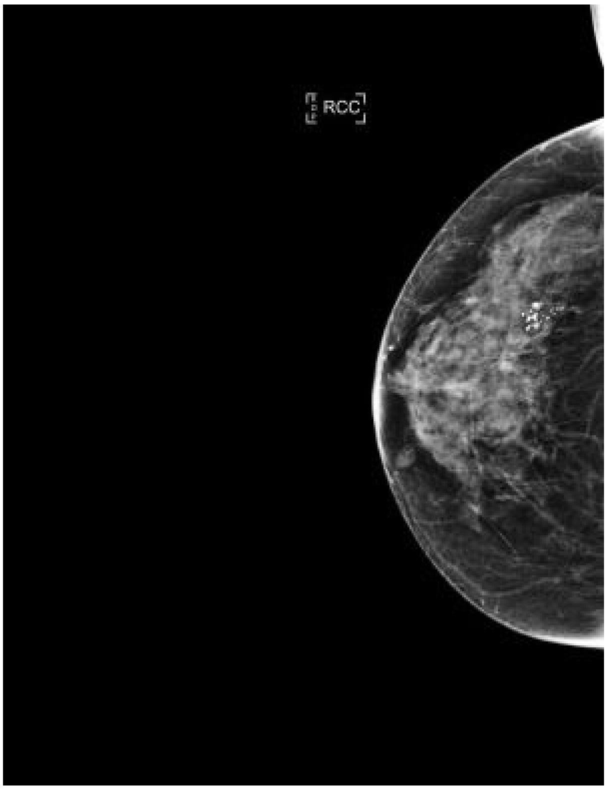

Figure 2.1: Example of a mamogram image (Adapted from [14])

When a radiologist examines a mammogram, they are searching for subtle clues that may indicate the presence of breast cancer. The interpretation process is both nuanced and complex, requiring a deep understanding of the various features that can be present within the image.

One key area of focus is the detection of calcifications - small deposits of calcium that can accumulate within the breast tissue. These tiny formations can often be indicative of cancer, particularly when they appear in a characteristic pattern or are associated with other suspicious findings. In addition to calcifications, radiologists also look for masses - solid or cystic lesions that may indicate the presence of a tumor. Densities - areas of increased breast density - can also be an area of concern, as these can be caused by fibrosis (scarring), inflammation, or even cancer. Finally, radiologists will examine the symmetry and shape of the breasts, searching for any signs of asymmetry that may indicate an underlying issue.

While mammography has been a powerful tool in the detection of breast cancer, it is not without its limitations. One major concern is the issue of false positives - benign lesions are often identified as suspicious, leading to unnecessary biopsies and subsequent anxiety for patients.

Conversely, some cancers may be missed altogether due to their small size or location within the breast. This can be particularly problematic in women with dense breast tissue, who may be at higher risk for false negatives [15]. Furthermore, mammography sensitivity can vary by age and ethnicity, with younger women and those of African descent being at higher risk for false negatives [13]. It is also important to consider the factor of human error in the analysis of these sets of images.

2.1.2 Ultrasound

Ultrasound imaging has become an increasingly important tool in the assessment of breast lesions, particularly in conjunction with mammography and other diagnostic modalities. Ultrasound uses high-frequency sound waves to create images of structures within the body, allowing for real-time visualization of the breast tissue [16].

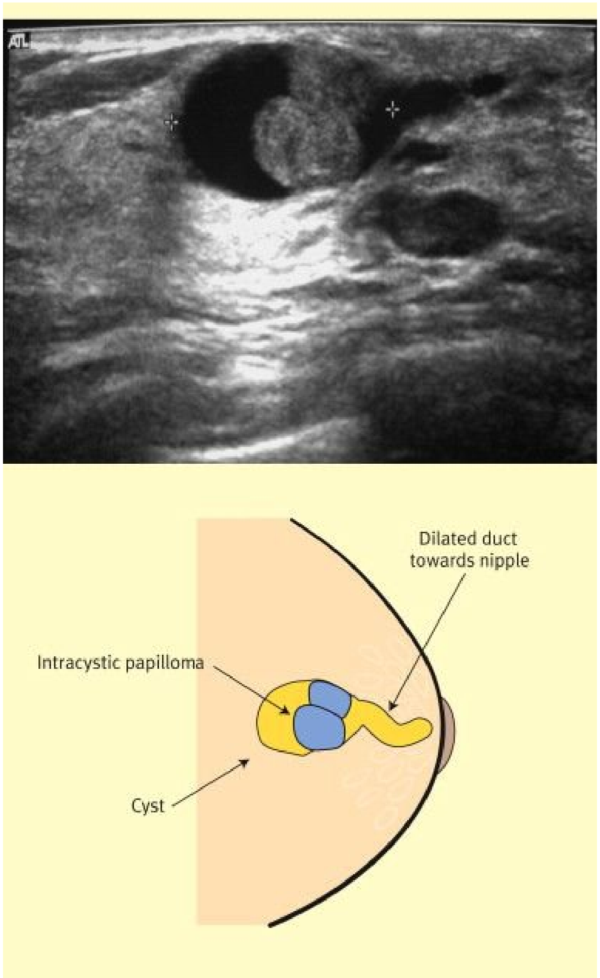

Figure 2.2: Example of a Mammogram (Adapted from [17])

One of the key strengths of ultrasound is its ability to characterize lesions, distinguishing between benign and malignant growths. This enables clinicians to develop targeted treatment plans that maximize patient outcomes. Moreover, ultrasound provides precise measurements of tumor size, which is essential for determining the most effective course of treatment. In addition to these benefits, ultrasound can also guide biopsy procedures, ensuring that tissue samples are obtained with precision and accuracy. By reducing the risk of complications and improving diagnostic yield, ultrasound plays a critical role in the early detection and treatment of breast cancer [18].

Despite its many advantages, ultrasound is not without limitations. The quality of ultrasound images depends heavily on the skill and experience of the operator, which can lead to variations in image interpretation. Furthermore, ultrasound waves have limited penetration depth, making it challenging to image deeper structures within the breast [19].

2.1.3 Thermogram

As a relatively new technology in breast imaging, thermography is a non-invasive imaging modality that uses heat signatures to detect breast abnormalities. This technique has gained popularity in recent years due to its ability to provide a unique perspective on breast health. It relies on the principle that abnormal tissues, such as tumors, exhibit altered blood flow and metabolism. As a result, these areas produce increased heat signatures compared to normal tissue. The thermographic camera captures these heat patterns, providing a visual representation of thermal activity within the breast [20].

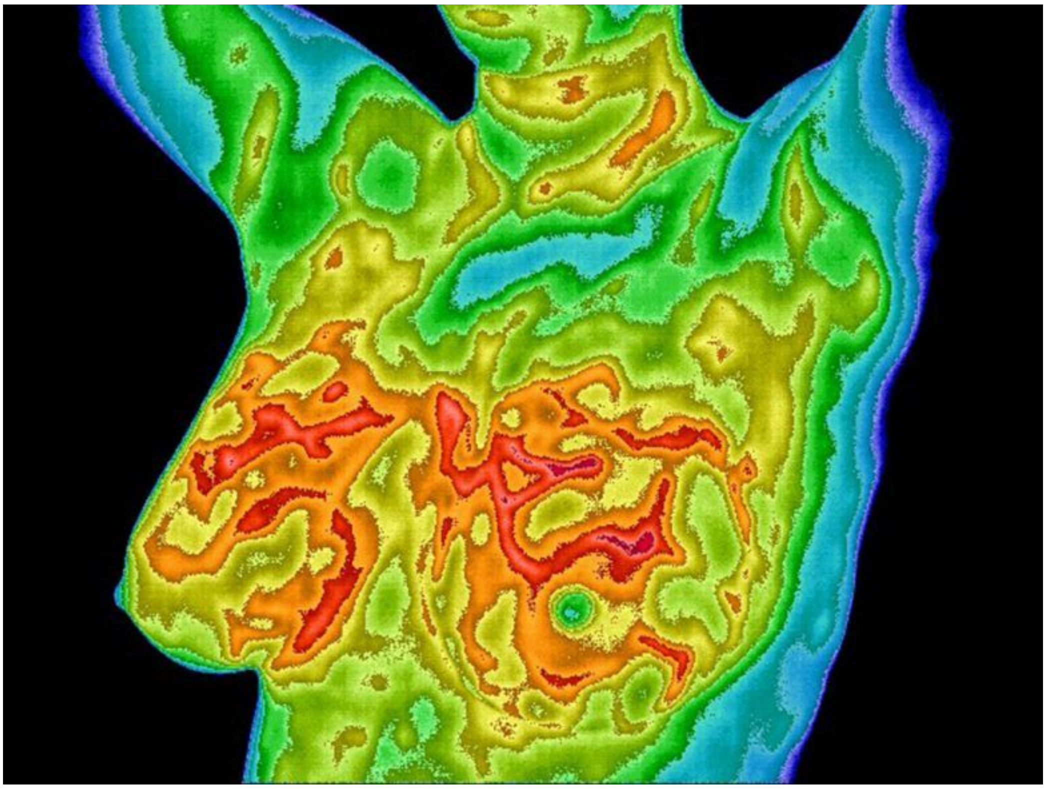

Figure 2.3: Example of a thermogram image. (Adapted from [21])

While thermography has shown promise in detecting breast abnormalities, its use is not without challenges. Several limitations and controversies have been raised regarding its sensitivity and specificity, operator variability, and regulatory status [22].

As with the other methods mentioned before the quality of thermographic images can be influenced by a range of factors, including the skill level of the operator. Beyond human factors, external elements such as ambient temperature, patient positioning, menstrual cycle variations, and the application of creams or lotions can influence thermographic results, potentially affecting both accuracy and reproducibility. This variability may impact diagnostic accuracy, emphasizing the need for more effective image acquisition techniques [23]. Researchers are actively exploring ways to enhance the sensitivity and specificity of thermography, as well as its regulatory recognition, therefore an integration with some kind of computer aided technique would be beneficial to the scientific research community of this topic [24].

2.1.4 Tomosynthesis

Breast tomosynthesis, also known as **Digital Breast Tomosynthesis (DBT)**, is a cutting-edge imaging modality that has revolutionized the field of breast imaging. This advanced technique offers several benefits over traditional mammography, making it an essential tool in modern breast cancer screening and diagnosis [25]. It works by capturing multiple low-dose X-ray images from different angles around the breast. These images are then reconstructed into a 3D dataset, allowing for detailed visualization of breast tissue. This technique enables clinicians to evaluate the breast in thin slices, reducing the overlap and artifacts that can occur with traditional mammography [26].

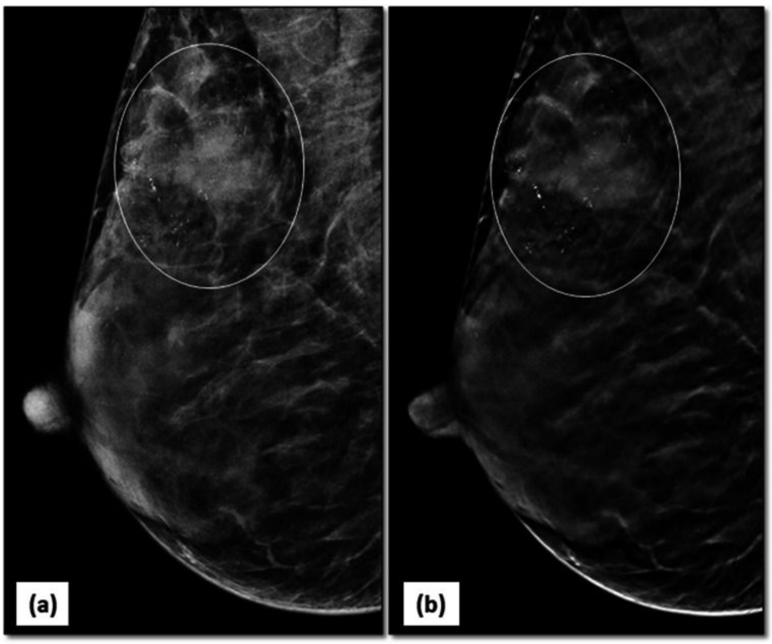

Figure 2.1: Example of a tomosynthesis 3D image (Adapted from [27])

Tomosynthesis has certainly revolutionized the field of breast imaging, but it's not without its challenges. One of the main concerns is the high upfront cost of purchasing a tomosynthesis system, which can be a significant barrier for some medical facilities. Additionally, while tomosynthesis uses lower doses of radiation than traditional mammography, the cumulative exposure over time can still be a concern for patients [26].

Interpreting tomosynthesis images requires a high level of expertise, and clinicians need to undergo specialized training to get the most out of this technology. The sheer volume of data generated by tomosynthesis can also be overwhelming, making it difficult for some clinicians to accurately interpret results. Because of this, this method is also influenced by human factors [6].

2.1.5 Histopathology

Histopathology has been a cornerstone of cancer diagnosis for decades, but recent advancements in technology have transformed this field into a dynamic and rapidly evolving discipline [28].

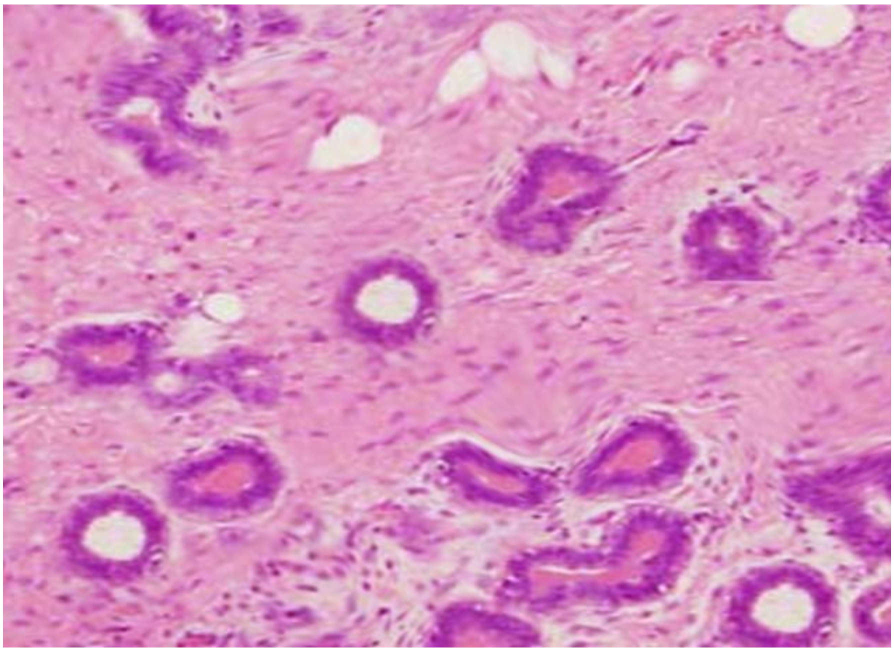

Figure 2.1: Example of a histopathology image (Adapted from [29])

Unlike all the other methods referenced before in this chapter, histopathology provides a detailed examination of individual cells instead of focusing on mass detection, allowing pathologists to identify subtle abnormalities and diagnose cancer with unprecedented accuracy. The advent of digital slides has streamlined diagnostic workflows, enabling pathologists to access high-quality images from anywhere in the world. This shift towards digital pathology has also facilitated collaboration among experts, enabling them to share knowledge and best practices more efficiently [30]. The development of *virtual staining* technology has eliminated the need for physical samples, reducing costs and increasing efficiency. Moreover, AI-powered algorithms can automatically detect tumor boundaries, differentiate between cancerous and benign tissue, and even predict disease progression and treatment response at the cellular level [31].

High-quality images and meticulous annotation are essential for accurate diagnoses, but even with these in place, human factors can still impact results. Pathologists, like any other professionals, are susceptible to fatigue, stress, and variability in judgment, which can lead to errors in interpretation [30].

The integration of multiple systems and platforms is also a significant concern, as the lack of standardization in hardware and software can create obstacles to seamless collaboration. This lack of standardization is particularly evident when considering the various digital pathology platforms currently available on the market, each with their own proprietary formats and interfaces [32]. As such, this thesis aims to contribute to the development of standardized protocols for data collection, annotation, and analysis, which will enable more efficient and effective communication between different systems and stakeholders.

2.2 Deep Learning

As mentioned before, the analysis of medical images is a complex task that requires a high degree of accuracy and attention to detail. In recent years, researchers have explored various approaches to improving image analysis, including the use of deep learning techniques. This chapter will examine the application of deep learning methods to conventional examination modalities used in breast cancer screening, such as mammography, ultrasound, DBT, thermography and histopathology.

Deep learning models have been found to possess several key characteristics that make them particularly well-suited for medical imaging applications. For example, they are able to extract complex patterns from data through a process of automatic feature extraction. This allows them to identify subtle abnormalities in images that may not be visible to the naked eye. Additionally, deep learning models can rapidly and accurately process large datasets without requiring explicit programming [31] [32].

This ability to automatically extract features from data has led to significant advancements in the field of medical imaging. Researchers have been able to develop models that outperform traditional machine learning approaches in tasks such as image recognition and classification. However, the integration of new technologies into clinical practice is a gradual process, requiring careful evaluation and validation before widespread adoption.

In the case of deep learning methods applied to medical images, researchers must consider several factors, including model interpretability, data quality, and regulatory frameworks, to ensure safe and effective implementation [3]. This chapter will provide an overview of the current state of research in this area, highlighting both the potential benefits and challenges associated with the use of deep learning techniques.

2.2.1 Application in Mammography

The application of deep learning techniques in mammography analysis has garnered significant attention in recent years, driven by the need for more accurate and efficient detection of breast cancer cells. One of the primary approaches employed is the use of **Convolutional Neural Networks (CNNs)**, which have proven effective in tasks such as lesion localization, detection, and classification. The success of CNNs can be attributed to their ability to automatically learn features from large image datasets, eliminating the need for manual feature extraction [1].

Researchers have leveraged pre-trained models, such as *AlexNet*, *ResNet*, *MobileNet*, and *EfficientNet*, as a starting point for fine-tuning in mammography analysis. This transfer learning approach has shown improved accuracy compared to training models from scratch. Additionally, data augmentation techniques are often employed to increase the size of training datasets, which is essential due to the scarcity of large, high-quality medical image datasets. Furthermore, advanced techniques like ***YOLO (You Only Look Once)***, Attention mechanisms, and ***Generative Adversarial Networks (GANs)*** have been utilized for simultaneous detection and classification of masses [12], while feature fusion methods, such as ***Deep Generalized Canonical Correlation Analysis (Dg-CCA)*** combined with ***Disentangled Variational Autoencoder (D-VAE)***, aim to maximize feature correlation across modalities [2].

When looking at raw result values, various studies have reported high accuracy rates, with one notable example being a fine-tuned residual network achieving improved accuracy and sensitivity rates of 93.15% and 93.83%, respectively. Additionally, a deep learning system for breast cancer screening demonstrated impressive results, registering high accuracy, recall, and ***AUC (Area Under the Curve)*** values of 0.960, 0.929, and 0.928, respectively [1].

The same researchers have also explored the use of attention mechanisms to enhance performance in mammography analysis. The same study incorporated an attention mechanism into *VGG16* with feature selection, resulting in a notable improvement in accuracy, achieving a rate of 96.07%. Furthermore, transfer learning techniques have been employed successfully in mammography, with one study demonstrating an enhanced DCNN yielding an accuracy rate of 82.5% [1].

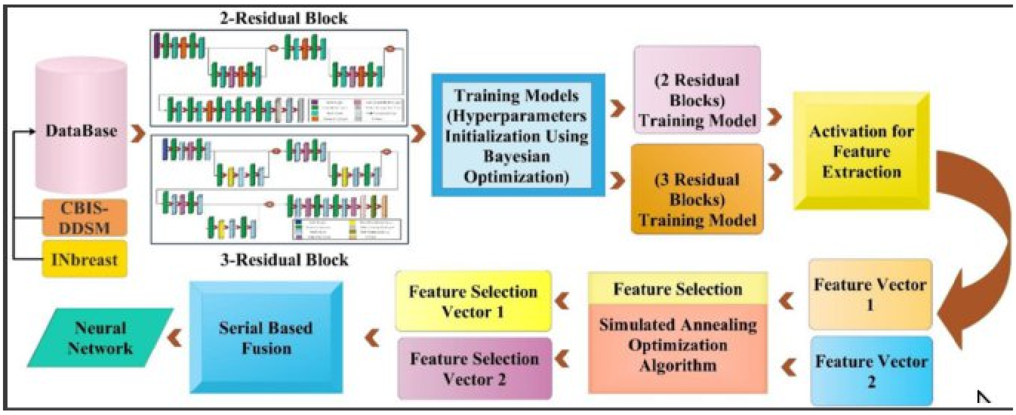

Figure 2.1: Suggestion of an implementation of a system to classify images. (Adapted from [1])

Other researchers made use of EfficientNet models has also shown exceptional performance, achieving an overall accuracy rate of 98.29% in classifying mammogram images into benign and malignant categories [33].

The development of two-stage deep learning methods has also led to significant increases in detection accuracy. For example, one separate study improved **mean average precision (MAP)** from 0.85 to 0.94, underscoring the potential of these approaches for improving breast cancer diagnosis and screening outcomes [34].

2.2.2 Application in Ultrasound

Recent advances in deep learning have revolutionized the field of ultrasound diagnostics. Specifically, Convolutional Neural Networks (CNNs) have emerged as a powerful tool for analyzing ultrasound images. As mentioned before, these networks excel at extracting high-level features from large-scale image datasets, making them an ideal choice for various tasks such as classification, recognition, object detection, and segmentation.

In this context, several CNN-based models have been explored and adapted for specific applications. Notable examples include *AlexNet*, *ResNet*, *MobileNetV2*, InceptionV3, Xception, NasNetMobile, VGG19, DarkNet-53, ShuffleNet, and SqueezeNet. Among these, *DarkNet-53* has garnered significant attention due to its exceptional performance in object detection tasks. Researchers have successfully modified this model using transfer learning, leveraging pre-trained weights to improve accuracy on ultrasound image classification tasks [1] [18].

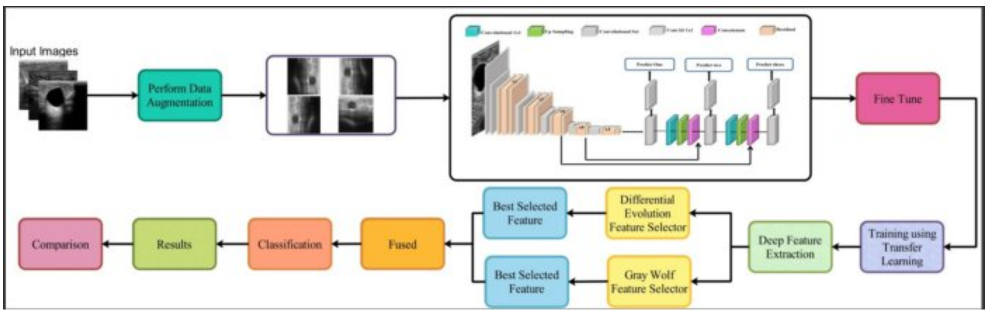

Figure 2.1: Proposed implementation off the framework employed in [18]. (Adapted from [18])

Segmentation is a critical step in ultrasound image analysis, allowing for precise location and extraction of areas with specific information. Hybrid approaches combining CNNs with **Recurrent Neural Networks (RNNs)** have also been explored to analyze temporal components in dynamic ultrasound image sequences. These models extract both spatial and temporal features, enabling researchers to better understand the dynamics of biological systems [1].

Some studies have demonstrated that DL-based computerized techniques can assist clinicians in detecting and classifying breast cancer correctly, while also enhancing image quality. For instance, one set of researchers were able to achieve impressive results by fine-tuning residual networks on large datasets, such as *CBIS-DDSM*, resulting in high accuracy and sensitivity rates of up to 93.83% and 96%, respectively [1].

Another notable achievement is the development of optimized 3D CNN models for automatic detection in **Automated Breast Ultrasound (ABUS)** images. These models have achieved remarkable sensitivities of up to 100% with an average of only 1.9 false positives per volume. Furthermore, a proposed framework combining DarkNet-53, feature selection, and probability-based fusion has achieved a best accuracy of 99.1% on an augmented BUSI dataset, while also significantly reducing computational time [3].

In the same study, researchers analyzed 20 other studies comprising 14,955 cases, reporting a combined sensitivity of 0.93 and specificity of 0.90 across all studies. Interestingly, multimodal ultrasound demonstrated superior performance compared to B-mode ultrasound alone. Additionally, researchers have also explored the potential of pre-training models on minimal datasets, which has been shown to improve accuracy by up to 14% [3].

Finally, some DL models have achieved remarkable results in breast cancer classification from ultrasound images. For example, the DeepbreastcancerNet model reached an impressive accuracy of 99.35% on a standard dataset and 99.63% on a binary dataset. These findings underscore the potential of deep learning-based computerized techniques to revolutionize breast cancer diagnosis using ultrasound imaging [36].

2.2.3 Application in Thermogram

The development of deep learning models has been a significant factor in enhancing the capabilities of thermography for breast cancer diagnosis. Yet again one of the most effective techniques employed in this field is the CNN. This architecture enables automatic extraction of visual features from thermographic images, reducing human error and increasing diagnostic accuracy.

Several CNN architectures have been developed to tackle specific challenges associated with thermography-based breast cancer detection. For instance, VGG models are notable for their simplicity and depth, making them effective in high-level feature extraction tasks.

ResNet models, on the other hand, leverage residual connections to build deeper networks that can capture complex visual patterns. DenseNet models incorporate dense connections to increase feature reuse and reduce redundancy, making them efficient for resource-constrained environments MobileNetV2 and Xception are other examples of lightweight CNN architectures that have been optimized for low computational requirements and memory constraints. These models enable real-time processing on mobile devices or other limited-resource platforms [37].

Other researchers employed InceptionNet to address specific challenges in thermography. These models utilize inception modules to capture multi-scale features, which are essential for detecting subtle temperature variations associated with breast tumors [38]. Simpler CNN architectures like AlexNet and GoogLeNet can be trained quickly but may not achieve the same level of performance as more complex models [22].

Ultimately, the choice of deep learning model depends on the specific characteristics of the dataset, computational resources available, and desired trade-off between accuracy and efficiency. Researchers have employed a range of techniques to optimize the performance of these models, including data augmentation, transfer learning, and hyperparameter tuning. For example, the first study where researchers utilized a ResNet-50 model reported an accuracy rate of 97.26%, as well as a EfficientNet-B7 that achieved an impressive 98.36% [37]. Other researchers of a seperate study proposed a EDCNN model that was able to achieve an accuracy of 96.8% and specificity of 93.7% [39]. A third set of researchers developed a combination of ResNet152 and Support Vector Machines (SVM) delivered an accuracy rate of 97.62% [40]. Another promising aproach was a MSADIDL model that demonstrated exceptional performance with an accuracy rate of 99.54% [41].

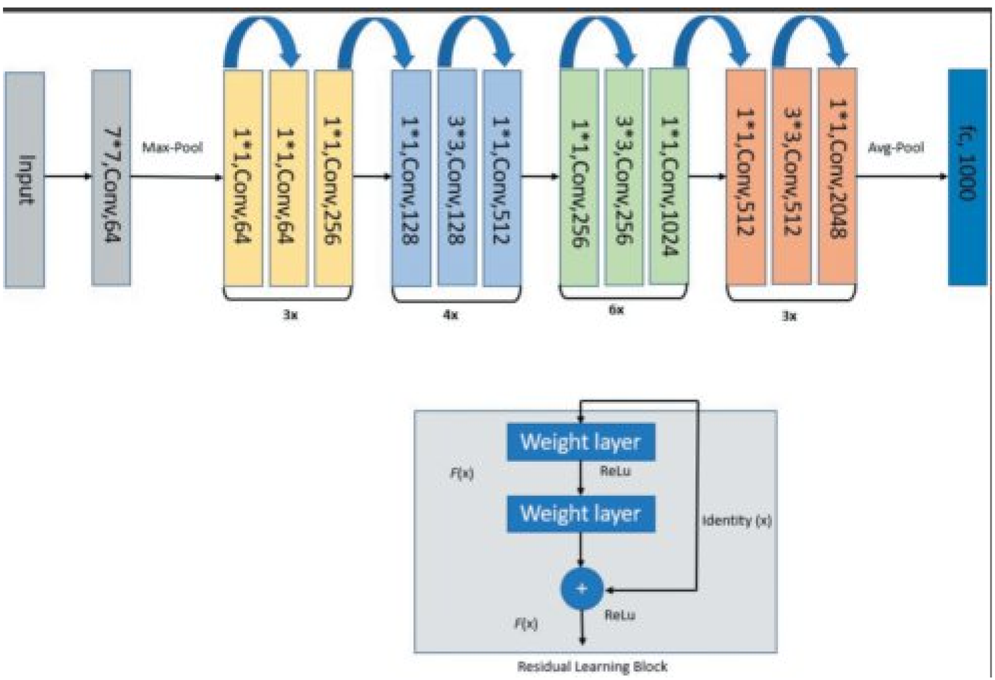

Figure 2.1: Example of a ResNet-50 architecture proposed on [37] (Adapted from [37])

Despite the encouraging results, several challenges persist in adopting thermography as a primary screening method for breast cancer detectio, one of them beign the limited availability and size of high-quality thermal imaging datasets pose significant challenges for model development and validation. Compared to mammography, thermographic data is relatively scarce, which can lead to overfitting and reduced generalizability of models [37].

2.2.4 Application in Tomosynthesis

The integration of deep learning techniques with **Digital Breast Tomosynthesis (DBT)** has been gaining significant attention in recent years. DBT, as a three-dimensional imaging modality, presents unique challenges in terms of data interpretation and analysis. The complexity of DBT images stems from the fact that they comprise multiple low-dose two-dimensional images stacked together to form a 3D dataset. This inherent complexity necessitates advanced image processing techniques to extract relevant features and improve diagnostic accuracy.

Despite it beign a relatively new technology, there as been a lot of efforts on the behalf of researchers to get the maximum potencial out of these sets of 3D images. A variety of architectures have been used, including convolutional neural networks (CNNs) such as AlexNet and VGG16, which have shown promising results in distinguishing between malignant and benign lesions. The same authors made use of transfer learning approaches with significantly improved classification performance in DBT images. For instance, **Multi-stageTransfer Learning (MSTL)** has been used to increase the area under the AUC from 0.85 to 0.91.
In addition to CNNs and transfer learning, they also employed **Graph Convolutional Networks (GCNs)** have also demonstrated high performance in malignant breast mass detection. Specifically, GCNs have reported a sensitivity of 96.20%, specificity of 96.00%, and accuracy of 96.10%. On top of this, they also employed a RetinaNet model combined with two-stage transfer learning achieved high true positive rates of 0.99 ± 0.02 [6].

Another set of researches of a separate study have developed the Deep-AutoMO model, a **Multiobjective Immune Neural Architecture Search (MINAS)** algorithm for model balancing and an **Evidential Reasoning based on Entropy (ERE)** approach for uncertainty estimation and robustness. This model has achieved a specificity of 0.8768, an AUC of 0.8925, and an accuracy of 0.8557, demonstrating its effectiveness in classifying breast lesions as benign or malignant [42].

Custom CNN models have also been developed to improve classification performance in DBT images. For instance, the 2-Residual Block CNN and 3-Residual Block CNN models, combined with **Bayesian Optimization (BO)** for hyperparameter initialization and **Simulated Annealing controlled Position Shuffling (SAcPS)** for feature selection, have achieved accuracies of 97.7% on the INbreast dataset and 97.3% on the CBIS-DDSM dataset [1].

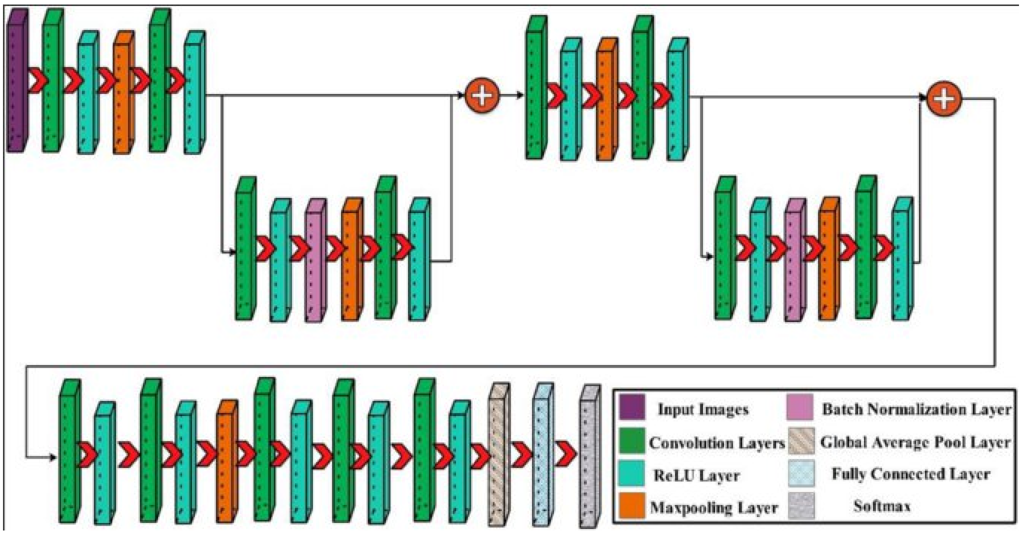

Figure 2.1: Proposed 2-Residual Block Architecture for classifcation of breast cancer. (Adapted from [1])

As with thermograms, despite the promising results, there are several limitations to the current state of DL models in DBT. One major challenge is the lack of standardized imaging protocols, which can lead to heterogeneity between studies. This makes it difficult to compare results across different datasets and hinders the development of more accurate and reliable models. There is also a need for larger and more diverse datasets to support the development of more accurate and reliable models applied to this context. Moreover, there is growing interest in integrating multiple sources of information, including textual data and structured medical knowledge, to enhance diagnostic accuracy and reasoning. This can be achieved through the use of LLMs (which will be covered in a future section) and knowledge graphs, which have the potential to reduce the need for extensive image data and improve model performance [6].

2.2.5 Application in Histopathology

The integration of deep learning techniques into histopathological analysis has sparked significant interest in recent years. This technology, which enables artificial neural networks to learn complex patterns from vast datasets, holds tremendous promise for automating and improving the efficiency and accuracy of breast cancer detection and classification. By leveraging DL's ability to mimic human brain information processing, researchers have developed **Computer-Aided Diagnostic (CAD)** systems that can quickly process large volumes of images and identify subtle details that might be missed by manual methods [31].

As with all of the other applications mentioned before CNNs are the most widely applied deep learning architecture for histopathological image analysis. Popular CNN models include AlexNet, VGG16 and VGG19, ResNet-18 and ResNet34, among others. These architectures have been widely adopted due to their ability to learn from large datasets and improve diagnostic accuracy. For instance, a study using the BreakHis dataset reported an average validation accuracy of 98.43% for 8-class classification and 99.72% for binary classification [30].

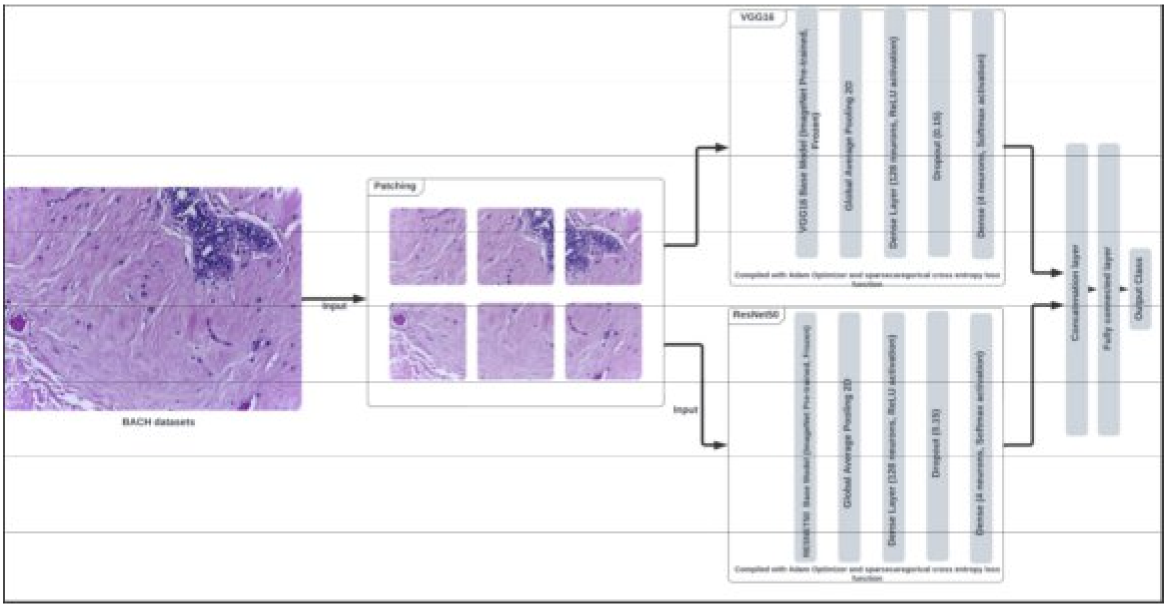

Figure 2.1: Schematic of the esemble model proposed in [30]. (Adapted from [30])

While CNNs have proven to be a powerful tool for this use case, researchers have also explored the potential of hybrid models that combine CNNs with traditional machine learning classifiers or other deep learning architectures. These innovative approaches include combining **Multilayer Perceptron (MLP)** for feature extraction and LightGBM for final classification, achieving high accuracy of up to 94% on certain datasets. Additionally, attention mechanisms have been incorporated into various models, such as Attention U-Net, Convolutional **Block Attention Module (CBAM)**, and **Squeeze-and-Excitation (SE)** attention mechanisms. These innovative approaches aim to enhance feature refinement by focusing on critical regions within tissue samples [28]. Other authors have also employed RNNs to analyze sequences of image patches or entire tissue slides, together with GNNs applied to model spatial relationships and patterns in tissue samples. Most recently, **Vision Transformers (ViT)** have been introduced to computer vision tasks, capturing global dependencies between image patches with impressive results on certain benchmarks [32].

Despite the significant advancements made in deep learning for histopathological image analysis, several challenges persist. The computational costs associated with training effective DL algorithms pose a barrier for smaller institutions, requiring sophisticated hardware platforms like high-end GPUs and substantial storage capacity. Additionally, the "black box" problem - where AI algorithms lack transparency into their decision-making process - makes it challenging for clinicians to trust and explain their diagnostic recommendations to patients. Standardization protocols for image acquisition, annotation, and analysis are also lacking, exacerbating these challenges [32] [43].

2.2.6 Some remarks on Deep Learning

2.2.6.1 Advantages of Deep Learning in Breast Cancer research

Deep learning has revolutionized the field of breast cancer diagnosis, offering a range of benefits that improve diagnostic accuracy, efficiency, and clinical outcomes. One of the most significant advantages of DL is its ability to enhance diagnostic accuracy and efficiency in medical imaging tasks such as segmentation and classification. By analyzing complex patterns in images, DL models can identify subtle details that may be missed by traditional methods, leading to earlier detection of tumors, even those that are very small.

In fact, has mentioned before, we can see that DL models can approach or surpass the performance of pathologists in breast cancer diagnosis. This is a significant achievement, as it highlights the potential for DL to augment and potentially replace human interpretation in certain medical imaging tasks. Moreover, DL performs end-to-end feature learning and classification directly from raw data, eliminating the need for manual feature selection. This automation enables healthcare professionals to focus on more complex and high-value tasks, while also reducing the workload associated with image analysis.

2.2.6.2 Challenges associated with research

Despite the advancements made in applying deep learning techniques to mammography analysis, several challenges remain. One of the most significant hurdles is the computational burden and processing time associated with high-resolution images, which can hinder the adoption of these technologies in clinical settings. Furthermore, there is a persistent need for large, diverse datasets that are collected using standardized protocols. This is crucial not only for training robust models but also for ensuring their generalizability across various datasets, vendors, and imaging acquisition techniques [34].

Another main concern is the scarcity and annotation of high-quality images required to train effective DL algorithms. The process of collecting and annotating large datasets is time-consuming, expensive, and often limited by patient confidentiality and privacy regulations.

The diversity and generalizability of models are also major issues, as most studies rely on single-center datasets that may not be representative of diverse populations, vendors, or imaging acquisition techniques. Furthermore, medical datasets frequently suffer from heterogeneity (e.g., varying image resolutions, staining methods) and class imbalance, leading to biased models. These challenges underscore the need for more comprehensive, standardized, and annotated datasets that can accurately reflect real-world clinical scenarios.

2.2.6.3 The future of Deep Learning in Breast Cancer Research

To overcome the challenges mentioned in the earlier chapter, researchers must focus on refining deep learning algorithms to improve model interpretability and accuracy. Future directions include developing real-time clinical deployment frameworks that can incorporate real-time image analysis for faster diagnoses [35].

There is also interest in exploring the potential of machine learning algorithms for automating clinical tasks and improving patient outcomes. However, their effective deployment requires addressing limitations such as data quality issues, bias in training datasets, and domain-specific knowledge gaps.

The integration of AI-based breast density assessments with other features, such as patient demographics and medical history, holds promise for developing more accurate risk prediction models. To ensure the safe and responsible use of AI in breast cancer analysis, researchers must prioritize developing robust validation frameworks and governance mechanisms that address concerns around data privacy, accountability, and transparency.

Ultimately, as researchers continue to explore new frontiers in DL applications, the integration of LLMs is projected to play a pivotal role in augmenting human capabilities. LLMs like ChatGPT and Gemini can serve as adjunct informational tools for patients and healthcare professionals, streamlining clinical workflows, supporting multidisciplinary meetings, and aiding in report generation.

2.3 Large Language Models

LLMs are rapidly gaining traction in the field of breast cancer detection and management, extending beyond the capabilities of traditional Deep Learning methods. They are Deep Learning models designed to comprehend and generate meaningful responses, often trained on vast datasets, allowing them to capture deep linguistic and semantic relationship. Using LLMs instead of or in addition to Deep Learning for breast cancer identification and classification offers several distinct advantages, primarily due to LLMs' advanced capabilities in natural language processing and multimodal integration, though they also come with their own set of limitations [9].

Figure 2.1: Ollama LLM platform icon. (Extracted from [8])

2.3.1 Advantages of using LLMs

The traditional approaches to analyzing medical reports, particularly those related to breast cancer detection, have been hindered by variability in linguistic style, formatting, abbreviations, negations, and contextual nuances. These complexities necessitate a deep understanding of medical and clinical knowledge, which can be resource-intensive and expensive. In recent years, Large Language Models (LLMs) have emerged as a game-changer in this domain. By leveraging vast datasets, LLMs can comprehend textual information and generate meaningful responses, thereby capturing deep linguistic and semantic relationships. This transformative approach has significantly simplified the development process, reducing dependency on extensive rule-based programming [44]. Specialized LLMs like CancerLLM have demonstrated exceptional performance in extracting specific cancer phenotypes and generating diagnoses from clinical notes and pathology reports [45].

Multimodal LLMs, which can process both text and images simultaneously, have revolutionized image analysis. These models create a joint embedding space for meaningful representation, enabling direct image analysis and tumor classification with high accuracy (e.g., 92% in breast cancer diagnosis when integrated with CNNs). This has the potential to enhance semantic understanding of visual content by interpreting and generating textual descriptions [10].

LLMs can also provide valuable decision-making support tools for referring physicians. By recommending appropriate imaging examinations, LLMs can optimize resource allocation and reduce unnecessary procedures. Moreover, they can assist in classifying the clinical significance of breast pain symptoms, potentially streamlining patient triaging in busy clinics. The role of LLMs extends beyond individual clinicians; they're also being explored as a tool to facilitate multidisciplinary meetings (tumor boards). By synthesizing complex information and offering evidence-based recommendations, LLMs can help navigate the complexities of treatment guidelines and inform decision-making processes [5] [46]. These models can also serve as valuable adjunct informational tools for breast cancer patients, providing guidance on general inquiries and explaining complex medical concepts in plain language. This empowering approach fosters better communication and compliance by breaking down the barriers to understanding that often accompany medical jargon. Some LLMs, like ChatGPT, have even demonstrated a remarkable ability to convey empathy through their responses, which could help alleviate patient anxiety [5][9].

Relatively to money spending, developing custom LLMs within an institution can be a game-changer for those seeking to leverage AI technology while minimizing costs and ensuring data security. By fine-tuning open-source models, such as BURExtract-Llama which is based on Llama3-8B, institutions can achieve comparable performance levels to proprietary models like GPT-4 without shouldering the burden of hefty expenses or compromising patient confidentiality when handling sensitive Protected Health Information (PHI). This approach enables organizations to overcome a significant hurdle in developing effective AI systems: accessing and annotating large-scale, high-quality clinical datasets without exposing themselves to potential financial or privacy risks associated with commercial Large Language Models [7].

2.3.2 Challenges associated with the use of LLMs

While LLMs have shown promise in breast cancer care, it is essential to acknowledge their limitations. One significant challenge is the potential for hallucinations, where LLMs generate incorrect or fabricated responses. This can manifest as non-existent breast imaging categories, inaccurate cost information, or false study citations, which can have serious consequences in clinical decision-making [9].

Also, general-purpose LLMs often lack nuanced domain-specific knowledge, particularly when it comes to highly specialized issues like breast cancer treatment recommendations. These models may misinterpret complex medical concepts, leading to suboptimal decisions. Moreover, they may struggle with understanding the context and subtleties of clinical questions, which is critical in healthcare [9]. Still related to this, many LLMs operate as "black boxes," making it challenging to understand the reasoning behind their decisions. This lack of transparency hinders clinician trust and adoption, as clinicians need to be able to rely on the accuracy and reliability of these models. Without a clear understanding of how an LLM arrives at its conclusions, it is difficult to verify its results or identify potential biases [11].

Another issue is that current multimodal LLMs may struggle with direct visual data interpretation, achieving lower accuracy than human radiologists in interpreting complex medical images, especially for imaging-dependent questions. While some progress has been noted, human experts still outperform LLMs in many visual diagnostic tasks. Enhancing the ability of LLMs to interpret and analyze visual data is essential for accurate decision-making [5]. LLM responses can also show variability and inconsistency, even with identical inputs, which raises concerns about clinical reliability. Misspellings and abbreviations in clinical notes can significantly impact their performance, emphasizing the need for high-quality input data. Furthermore, some LLM versions may exhibit a declining accuracy over time despite updated data access, highlighting the potential risks of uncontrolled input sources [45] [47].

For some parties, there is also the issue of privacy concerns. Handling **Protected Health Information (PHI)** raises significant privacy concerns in breast cancer LLMs. The data used to train many major LLMs are not publicly available, making accurate validation of the information impossible. Addressing legal and ethical questions concerning privacy, data security, and liability is crucial for ensuring responsible use of these models [9].

Deploying LLMs with billions of parameters presents significant computational challenges for hospitals or medical institutions with limited resources. These models require substantial computing power and infrastructure for effective training and deployment, posing financial and technical barriers to widespread adoption. Moreover, the performance of LLMs can be highly dependent on the quality and specificity of the prompts used, emphasizing the need for sophisticated prompting models tailored to specific oncologic entities [45].

Finally, we also have the fact that LLMs primarily rely on static, historical data and may not incorporate real-time updates of emerging evidence or the latest clinical guidelines. This lag can be a significant drawback in rapidly evolving fields like medicine, underscoring the need for more dynamic and adaptable models that can seamlessly integrate new information [5].

2.3.3 The future of LLMs in breast cancer research

As we look toward the future, the integration of Large Language Models (LLMs) into breast cancer care is envisioned as a path towards increased sophistication and efficiency. The goal is not only to enhance decision-making but also to improve patient-centered care through more streamlined workflows. A crucial aspect of this vision is maintaining human oversight, ensuring that clinicians remain at the forefront of medical decisions.

The next generation of LLMs will likely involve advanced multimodal integration, combining diverse forms of data such as images, videos, voice, and text to provide a more comprehensive picture of the patient. This could involve analyzing exam images alongside patient history and voice recordings for more accurate diagnoses. The potential benefits include not only enhanced diagnostic accuracy but also improved patient outcomes through more tailored treatments. They will also assist surgeons by synthesizing complex information and providing evidence-based recommendations, leading to more effective treatment plans. This includes suggesting relevant guidelines and highlighting differences between sources, enhancing the precision of clinical decisions [5].

The continued development of in-house LLMs by fine-tuning open-source models offers a cost-effective and competitive alternative to proprietary solutions. The benefits include enhanced data privacy and reduced costs, allowing hospitals to adopt these models without significant financial strain. This shift towards more accessible and adaptable LLMs will enhance their integration into clinical practice [7].

LLMs can become invaluable resources for ongoing medical education and training, offering simulated clinical experiences for learners to refine diagnostic reasoning and receive tailored feedback. They can enhance research equity, versatility, and efficiency in various aspects of healthcare, including breast cancer diagnosis and treatment. The ability of LLMs to learn from diverse real-life clinical data could lead to the development of more sophisticated and widely applicable classification systems for breast conditions, accounting for patient variability and nuances [9] [11].

Ultimately, the goal is for LLMs to augment human expertise, leading to more informed decision-making and a deeper understanding of patient needs, thus shaping the future of breast cancer care.

3

LET'S CREATE ANOTHER CHAPTER

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3.1.1.1 One Level Deeper

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JOHN DOE

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