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A novel approach in cancer diagnosis: integrating holography microscopic medical imaging and deep learning techniques—challenges and future trends

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Abstract

Medical imaging is pivotal in early disease diagnosis, providing essential insights that enable timely and accurate detection of health anomalies. Traditional imaging techniques, such as Magnetic Resonance Imaging (MRI), Computer Tomography (CT), ultrasound, and Positron Emission Tomography (PET), offer vital insights into three-dimensional structures but frequently fall short of delivering a comprehensive and detailed anatomical analysis, capturing only amplitude details. Three-dimensional holography microscopic medical imaging provides a promising solution by capturing the amplitude (brightness) and phase (structural information) details of biological structures. In this study, we investigate the novel collaborative potential of Deep Learning (DL) and holography microscopic phase imaging for cancer diagnosis. The study comprehensively examines existing literature, analyzes advancements, identifies research gaps, and proposes future research directions in cancer diagnosis through the integrated Quantitative Phase Imaging (QPI) and DL methodology. This novel approach addresses a critical limitation of traditional imaging by capturing detailed structural information, paving the way for more accurate diagnostics. The proposed approach comprises tissue sample collection, holographic image scanning, preprocessing in case of imbalanced datasets, and training on annotated datasets using DL architectures like U-Net and Vision Transformer(ViT's). Furthermore, sophisticated concepts in DL, like the incorporation of Explainable AI (XAI) techniques, are suggested for comprehensive disease diagnosis and identification. The study thoroughly investigates the advantages of integrating holography imaging and DL for precise cancer diagnosis. Additionally, meticulous insights are presented by identifying the challenges associated with this integration methodology.

1. Introduction

Medical imaging plays a vital role in detecting and diagnosing cancer by providing valuable insights into the presence, location, and characteristics of abnormalities within the body[1]. Multiple imaging modalities, such as 'Magnetic Resonance Imaging (MRI),' 'Computer Tomography (CT),' 'Ultrasound,' and 'Positron Emission Tomography (PET),' offer critical insights into the presence, precise location, and other characteristics of tumors within the body [2]. These imaging techniques are readily available, budget-friendly, associated with minimal radiation exposure, and provide rapid outcomes, making them suitable for regular screenings and initial assessments. However, it is essential to acknowledge that these techniques are limited to depth information, three-dimensional views of biological structures, or other detailed anatomical information. Thus, despite their simplicity and cost-effectiveness, these imaging methods have limitations in performing in-depth analysis in fields like biology and medicine. Although these imaging

techniques are also three-dimensional, however they do not consider both amplitude (intensity) and phase (angle information) details of the structure under consideration. Therefore, to surpass the constraints of existing techniques, three-dimensional holography microscopic imaging methods have proven promising solutions in various fields, particularly medicine, offering a more holistic approach to imaging and analysis. [3].

Denis Gabor's invention of holography in 1948 was a groundbreaking development in optics and imaging [4, 5]. A study by [6] utilized holography to analyze various attributes of pollen grains and monitor changes in neuronal morphology following exposure to hypotonic shock, demonstrating the significant capabilities of holography in advanced cell imaging. As mentioned earlier, traditional imaging techniques are limited in providing phase information. Therefore, three-dimensional holography microscopic imaging [7] techniques were introduced to overcome these limitations, offering a more comprehensive perspective. Integrating three-dimensional holography microscopic imaging and Deep Learning (DL) has marked a groundbreaking collaboration in medical diagnostics and research, offering an innovative approach to understanding complex biological structures. The most unfortunate aspect of a disease's progression into cancer is its late diagnosis, as early detection is often the key to effective treatment and improved results. Early diagnosis allows for precise assessment of associated risks and improves patient diagnosis. Artificial Intelligence (AI) plays a vital role in advancing early cancer diagnosis via its capacity to analyze diverse data sources such as 'medical images,' 'blood samples,' 'pathology samples,' and 'other medical records.' AI approaches contribute to early cancer detection by determining the most crucial advancing stage of the disease at its earliest [8]. Through this analysis, AI can potentially improve risk assessment, automating the identification of pre-cancerous (or early) stages and making the diagnostic process more efficient. DL, a subpart of AI, has proven remarkable progression in early cancer diagnosis through the utilization of models such as Convolutional Neural Networks (CNNs) [9], Recurrent Neural Networks (RNNs)[10] etc. These advanced DL models have proven highly effective in identifying early cancer stages due to their ability to analyze complex patterns and subtle features within medical images. Consequently, AI has significantly enhanced risk assessment and the rapid classification of tissue images as either 'benign' or 'malignant.' The future of AI and DL in early cancer detection shows great potential for enhancing diagnostic precision and benefiting patient care [11].

Holographic microscopy imaging stands as an essential breakthrough in the field of microscopy, offering a distinctive ability to record three-dimensional images that integrate not just an object's intensity, as seen in traditional imaging but also its depth characteristics (phase) using laser technology [12]. In contrast to conventional imaging, which primarily offers an intensity perspective, holography-based methodologies empower scientists to observe intricate structures from a three-dimensional vantage point. Within the domain of biological tissues, this comprehensive methodology demonstrates substantial utility across a range of scientific and medical contexts. It deepens one's insight into biological samples and complex microstructures by capturing a more detailed representation of the tissue. Integrating three-dimensional holographic microscopy and DL offers a novel approach to understanding complex biological structures and processes in medical diagnosis. This synergy will improve diagnostic precision and aid in the early detection of cancerous tissues, potentially saving human lives. Therefore, the integration of holography microscopic imaging with advanced DL methods presents an innovative approach in the field of medical imaging.

This research study is conducted by reviewing a number of research articles with the following objectives:

- To offer an extensive examination of the current state-of-the-art in utilizing holography microscopy in combination with DL for cancer detection.
- To provide an in-depth explanation of the principles and technologies involved in holography microscopic imaging, ensuring that readers understand the underlying concepts.
- To explore various challenges associated with this collaborative approach, such as dataset collection and other related issues.
- To examine different studies that use DL architectures and algorithms to analyze holographic medical images.
- To investigate numerous practical applications of this technology in the medical field for disease diagnosis.
- To discuss comprehensively the benefits of holography microscopic imaging, compared to traditional medical imaging methods typically utilized in oncology.

1.1. Motivation and contribution of this study

This review paper is motivated by the need to improve current practices in cancer diagnosis, given the challenges that traditional imaging methods face in achieving optimal accuracy, often resulting in delayed or inaccurate diagnoses. The study acknowledges the transformative impact of DL in medical imaging and comprehensively explores the growing significance of holography microscopic phase imaging. The research contributes by examining the interplay between DL

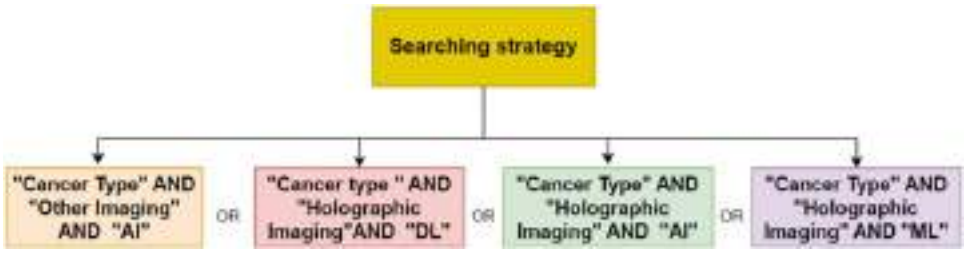

Figure 1. Paper searching query.

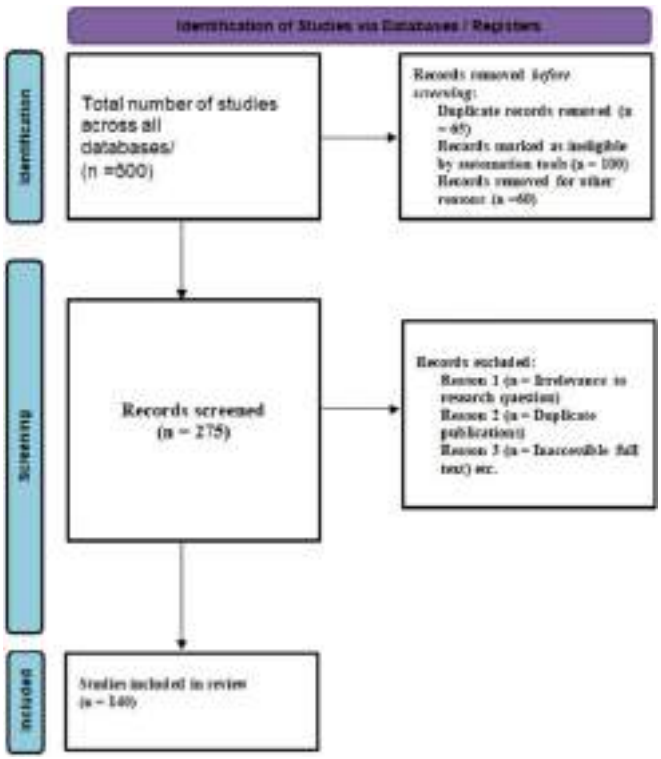

Figure 2. PRISMA diagram illustrating the study selection process.

and holography microscopic phase imaging in early cancer diagnosis. The objective is to thoroughly understand advancements, identify gaps, and propose future research directions in this collaborative field [13] by synthesizing and critically analyzing state-of-the-art approaches at the intersection of DL and holography microscopic phase imaging.

1.2. Paper searching strategy and article selection criteria

The search strategy utilized throughout this study is provided in figure 1 following the keywords 'holography,' 'DL,' 'ML,' 'AI,' 'early diagnosis,' 'cancer diagnosis,' and 'Quantitative Phase Imaging (QPI).' For this review study, *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* guidelines[14] is followed, a recognized systematic review framework, to identify and evaluate relevant studies systematically, improving the credibility and reliability of the analysis depicted in Figure 2. The PRISMA strategy aids in setting precise criteria for article selection, ensuring that systematic reviews and meta-analyses uphold transparency and rigor. This research study comprised three phases: identification, secreening, and evaluation. Initially, 300 papers were identified. After assessment, 275 were chosen by eliminating redundant or irrelevant papers. Finally, 140 relevant papers were selected following a thorough review.

The rest of this paper is organized as depicted in Figure 3. The paper begins with section 1, providing an introduction, followed by section 2, discussing related work, Section 3 describing holographic imaging and its principles. section 4 elucidates the role of DL and holography microscopic imaging in disease diagnosis, while section 5 presents the methodological approach to integrating holography microscopic imaging and DL. Section 6 highlights the benefits of the integrative

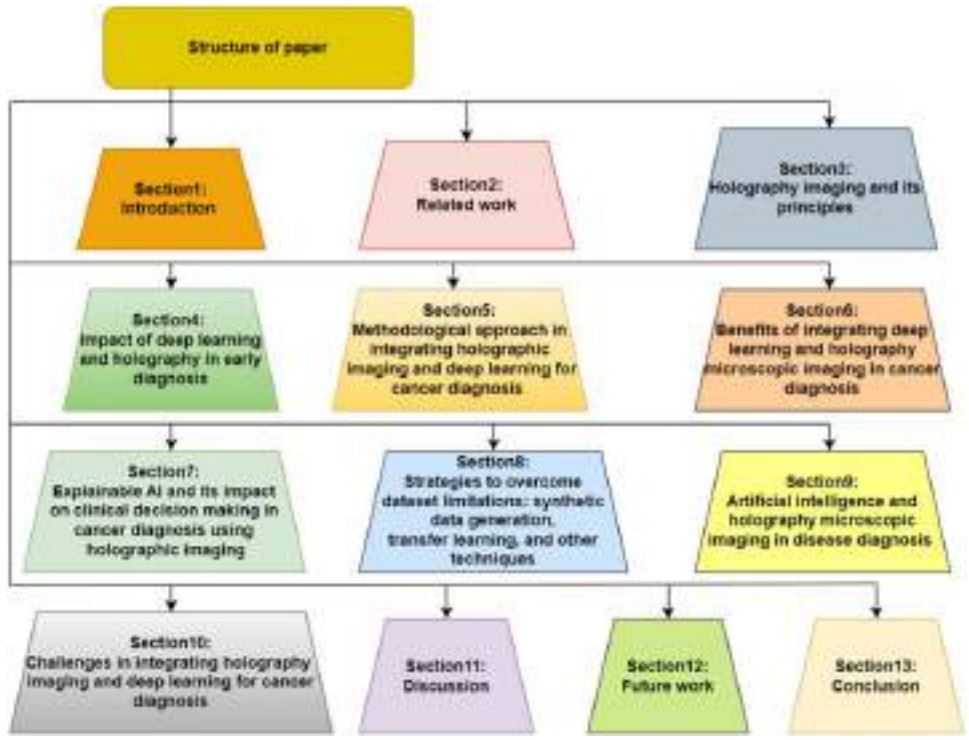

Figure 3. Structure of this study.

approach for early disease/cancer diagnosis. Section 7 discusses the impact of Explainable AI (XAI) on clinical decision-making in cancer diagnosis using holographic imaging. Section 8 follows with strategies to overcome dataset limitations, such as synthetic data generation and transfer learning. Section 9 offers a comprehensive description of integrating AI and holography microscopic imaging in disease diagnosis, further divided into subsections: ML and holography for disease diagnosis, DL and holography for disease diagnosis, transfer learning and holography for disease diagnosis, and finally, holography microscopic imaging and AI in cell imaging. Section 10 thoroughly examines the challenges of integrating holography imaging and DL for early disease diagnosis. Section 11 involves discussion, section 12 outlines future work, and section 13 concludes the study. The next section of the paper discusses the related work in this integrative field.

2. Related work

This section highlights the key concepts required to understand the integration of holography microscopic imaging and DL techniques in medical diagnostics. We begin by examining the role of holography in medical imaging, highlighting its strengths in the detection and analysis of particular disease. Next, we explore the role of computer vision techniques in medical imaging, emphasizing its significant influence on image analysis and diagnostic processes. Furthermore, the integration of holography and computer vision techniques is explored, emphasizing their combined potential to enhance diagnostic accuracy and effectiveness. Finally, recent trends and challenges in this novel combinational approach are examined. The focus is on recent advancements and the challenges hindering the progress of these technologies in clinical practice, so that future researchers can explore their work in this novel integrative field.

2.1. Holography in medical imaging

Holography has become an emerging imaging technique in medical diagnostics, allowing for high-resolution, three-dimensional imaging without direct interaction with the sample [15]. Holography uses light to capture and reconstruct images, allowing biological tissues and cells to be visualized in their natural, unstained form. This technique eliminates the need for staining, which might modify the sample, thereby offering a more precise view of cellular structures. As a result, holography contributes to improved disease detection and diagnostic precision. The findings in [16] underscore that digital holographic imaging provides substantial benefits for medical diagnostics and cellular analysis. The specialized holographic microscope enables high-resolution cellular examination with nanometric precision, allowing for accurate biomarker identification without staining. Conventional three-dimensional imaging techniques typically do not capture both amplitude and phase information. In contrast, holography provides detailed three-dimensional images, incorporating both amplitude and phase data without the need for staining. This helps maintain the sample's inherent

properties, ultimately improving diagnostic precision. Holography is, therefore emerging as a precise, quantitative alternative for clinical and research imaging. When combined with computer vision, it can greatly enhance diagnostic accuracy and help advance future medical research [17].

2.2. Computer vision in medical imaging

Computer vision is a field of AI that enables machines to interpret and analyze visual information from images (MRI, PET, CT, etc) or videos to generate meaningful insights. Computer vision is transforming the field of medical imaging, introducing advanced techniques that improve diagnostic accuracy and facilitate data-driven clinical decision-making. Computer vision reduces the workload for healthcare professionals by automating medical image analysis and improving the precision of disease detection [18]. Recent advances in ML and DL have enhanced computer vision for medical image analysis, but practical implementation in healthcare is still limited. The study by [19] highlights the significant progress made in computer vision, image processing, and pattern recognition in recent years, particularly in the field of medical imaging. These advancements have greatly strengthened the role of medical imaging in healthcare, leading to improved diagnostic precision and better patient outcomes. Their study presents a compilation of research and review articles that aim to foster further exploration and address the challenges associated with integrating these technologies into clinical settings. A study by [20] reviews a decade of progress in AI and DL for medical applications, focusing on computer vision in imaging, video analysis, and clinical use. Their study emphasizes the progress made in CNNs and their use in fields such as cardiology, pathology, dermatology, and ophthalmology, while also proposing directions for future research. A study by [21] highlights the effectiveness of Hidden Markov Models (HMM) and Support Vector Machines (SVM) in detecting precancerous tissues. It notes that HMM performs particularly well in handling multiple classes and remains robust even in noisy data conditions. The generalized Hurst exponent is recognized as an effective biomarker for distinguishing different tissue grades. However, differentiating between grades I and II remains a challenge due to occasional misclassification errors. Their study suggests that wavelet preprocessing may improve SVM performance, pointing to future improvements in model accuracy. The integration of holographic imaging and computer vision techniques in medical diagnostics presents a novel approach that improves accuracy thereby facilitating advanced healthcare services.

2.3. Integration of holography and computer vision techniques in medical imaging

The integration of holographic imaging with computer vision techniques is advancing medical imaging, enhancing diagnostic precision thereby improving overall accuracy [22]. Their study integrates Deep Neural Networks (DNNs), specifically CNNs and Vision Transformers (ViTs), with digital holography to improve 3D pose estimation of micro-objects. A hybrid approach combining GedankenNet and UNet-like architectures has been employed to infer 3D poses. The GedankenNet outperforms Tiny-ViT in processing speed, highlighting its effectiveness as a regression tool. Their approach improves both the accuracy and speed of holographic imaging, particularly for microrobotics and applications that require precise 3D position tracking. [23] discusses the advancements in digital holography, an imaging technique that captures multidimensional data—such as 3D structures, dynamics, phase, and light properties—without the need for an imaging lens. Their study demonstrates how digital holography enables single-shot exposure capturing nonlinear and incoherent light, thereby expanding its applications across various fields. The study by [24] reviews advancements in learning-based Computer-Generated Holography (CGH) enabled by DL techniques. Their study outlines the principles and algorithms of CGH, thereby comparing DNN architectures such as U-Net, ResNet, and Generative Adversarial Networks (GANs), while also discussing recent advancements and future directions in the field. The integration of holographic imaging with computer vision shows considerable potential to improve medical diagnostics. However, overcoming practical and clinical obstacles is vital for ensuring its widespread adoption.

2.4. Strategic directions for integration

Recent advancements in holographic imaging and AI have significantly advanced fields like biomedical diagnostics, 3D imaging, and real-time data processing [25]. The integration of holographic imaging and computer vision allows for precise, real-time 3D visualization, enhancing diagnostic accuracy and object recognition. This integration facilitates the extraction of comprehensive multidimensional data, advancing applications in areas like medical imaging, robotics, and dynamic scene interpretation. Despite notable advancements, significant challenges remain for effective integration of holographic imaging and DL. A key challenge is the limited availability of large, unbiased datasets, especially in biomedical areas, which hinders DL model development and makes comparative studies difficult. Models frequently encounter challenges in generalizing and adapting across diverse domains, particularly when trained on specialized datasets or within controlled environments. Furthermore, many ML and DL models

function as 'black boxes,' posing significant challenges in their interpretation and refinement. Incorporating specialized knowledge from holography into these models is a challenging task. Moreover, the large volume of holographic data, combined with its substantial storage and transmission requirements, complicates processing, while lossy compression can degrade data quality. Also, with high computational demands of processing holographic data, along with the need for real-time analysis, pose challenges in resource-limited settings. Emerging fields like dynamic object tracking, 3D reconstruction, and drug discovery underscore the necessity for specialized models to tackle these challenges. Therefore, harnessing the full potential of holography with AI and ML demands progress in data acquisition, computational power, model transparency, and regulation. The next section of the paper delves into exploring holography imaging and the core principles governing holographic imaging techniques.

3. Holography imaging and its principles

'Holography' originates from 'holos,' meaning 'whole,' and 'graphein,' meaning 'to write.' This imaging technique captures a complete image, including both 'amplitude' and 'phase' of the object, utilizing interference patterns for accurate three-dimensional characterization. Unlike conventional imaging techniques, holography records an interference pattern, requiring a reconstruction process (involving diffraction) to generate a three-dimensional image with both 'amplitude' and 'phase' information. The holography imaging process involves two steps: hologram recording (using interference patterns) and hologram reconstruction (using the diffraction process) [25]. Holography microscopy integrates the principles of holography and microscopy to capture detailed three-dimensional images of the object under investigation. Essential principles associated with this approach include:

3.1. Generation of a reference and object beam

Holography imaging involves the utilization of a laser beam to produce coherent light. A part of this laser light is directed towards a 'beam splitter,' which divides it into the object beam and the reference beam [7]. The reference beam travels directly to the recording medium, providing a stable phase reference. The object beam illuminates the object, and the light scattered from the object then combines with the reference beam on the recording medium to form the hologram.

3.2. Interaction with the specimen/object

The object beam is directed onto the specimen or target object, interacting with it thereby causing light scattering. The scattered light contains details about the object's morphology and variations in refractive index [7, 25].

3.3. Interference pattern recording

The recording of the interference [26] pattern occurs through the overlapping of the reference beam and the scattered object beam. This pattern contains information about both the phase and amplitude of the scattered light waves [27].

3.4. Recording plate

Interference takes place on the holographic plate coated with light-sensitive material. When light interacts with it, a chemical reaction initiates, and the light's intensity influences the outcome. A shutter is required to control light exposure duration preventing overexposure or underexposure, ensuring high-quality holographic images [27].

3.5. Process of reconstruction

A laser beam, typically originating from the same coherent source that produced the reference beam, is directed onto the stored interference pattern on the holographic plate to view the holographic image. When the reference beam interacts with the stored interference pattern, it regenerates a virtual three-dimensional representation of the specimen (via diffraction process) [28], available for viewing and analysis. A 'neutral density filter' is utilized in holography to control light intensity precisely, enhancing fringe visibility and modulation depth. It helps in equalizing the intensity of both light beams, particularly the fainter one resulting from the object scattering onto the holographic plate. Moreover, mirrors are crucial in accurately positioning and aligning the beams, assuring a consistent holographic image [25, 27]. The mathematical representations of the object wave, denoted as O(x, y), and the reference wave, represented as R(x, y), are expressed in equation 1 and 2 respectively as follows:-

$$O(x, y) = O_0(x, y)e^{j\delta_0(x,y)} \quad (1)$$

$$R(x, y) = R_0(x, y)e^{j2\pi f_R y} \quad (2)$$

Where, O_0 is the amplitude of the object wave, δ_0 serves as the phase component of the object wave encompassing essential information about the object being imaged. R_0 is the amplitude of the reference wave, $2\pi f_R y$ is the phase of the reference wave with no information about the object. $f_R = \frac{\sin\theta}{\lambda}$ represents the spatial frequency.

The object and reference waves intersect at the recording plane, generating an interference pattern. Their interaction involves constructive and destructive interference based on their phase relationships, resulting in diverse intensities on the holographic plate. This resultant interference pattern retains crucial amplitude and phase details, integral for the subsequent reconstruction of a three-dimensional image.

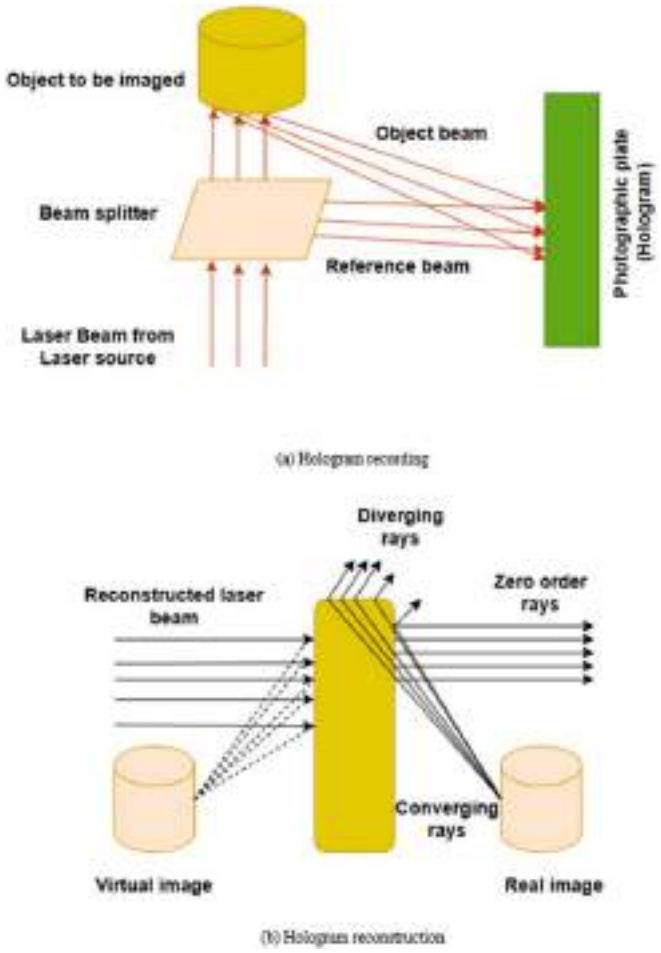

Figure 4. Overall holography principle.

Equations 3 and 4 represent the mathematical representation of the interference pattern.

$$A(x, y) = O(x, y) + R(x, y) \tag{3}$$

$$I(x,y) = |O(x,y) + R(x,y)|^2$$

$$I(x, y) = |O_0(x, y)|^2 + |R_0(x, y)|^2 + 2O_0(x, y) \times R_0(x, y)\cos(2\pi f_R y - \delta_0(x, y))$$

$$I(x, y) = |O(x, y)|^2 + |R(x, y)|^2 + O^*(x, y)R(x, y) + R^*(x, y)O(x, y) \tag{4}$$

Figure 4 illustrates the intricate concept underlying holographic imaging with (a) Hologram recording and (b) Hologram reconstruction. Traditional film-based holography imaging, as discussed above, relies on the direct exposure of holograms onto photographic film. This method boasts several advantages, notably high resolution and producing a tangible, permanent record. However, it comes with drawbacks, such as time-consuming chemical processing and the need for specialized equipment. On the other hand, modern camera-based holography [29] replaces film with digital cameras, allowing real-time feedback during hologram capture and facilitating digital processing. Camera-based holography imaging offers several benefits compared to traditional film-based methods. It provides real-time feedback during hologram capture, enabling users to make immediate adjustments for optimal results and facilitating faster experimentation. The digital processing capabilities inherent in camera-based systems allow precise control over reconstruction parameters and the application of computational techniques to improve image quality. The accessibility and user-friendly nature of digital cameras make camera-based holography more practical for a broader range of users. Furthermore, the versatility of camera-based systems allows for the implementation of advanced holographic techniques, and enhances experimental abilities, thereby enabling more comprehensive analysis, making them valuable tools for research, education, and various applications [30].

In general, holography microscopy offers several essential advantages in medical imaging by providing high-resolution three-dimensional imaging and supplying crucial depth information for understanding complex biological structures. This imaging technique significantly reduces occlusion effects by capturing multiple perspectives of the observed scene, furnishing a more comprehensive context. It has demonstrated promising outcomes in the medical field, particularly in characterizing images as 'cancerous' or

'non-cancerous' [31]. The subsequent section of the paper elaborates on the pivotal role that holographic imaging and DL play in achieving precise disease diagnosis.

4. Impact of deep learning and holography in early disease diagnosis

Holography microscopic imaging can advance future pre-operative surgical procedures by providing real-time, high-resolution visualization of microscopic biological structures, thereby improving diagnostic accuracy [32]. This cutting-edge technology furnishes a comprehensive three-dimensional insight into structures, assisting surgeons in making informed decisions before entering the operating room. A notable advancement in this field has been introduced by an Israeli firm, presenting three-dimensional holographic technology, revolutionizing how physicians perceive patient anatomy during surgical interventions. Through successful trials involving holographic simulations of beating hearts, medical professionals can now utilize a system that allows the observation of hyper-realistic three-dimensional holograms. This breakthrough will enable doctors to conduct procedures based on X-ray, MRI, or ultrasound data, projecting holographic images onto a fixed point in space for advanced visualization [33]. State-of-the-art algorithms facilitate higher accuracy, aiding healthcare professionals in precise examinations and adequate treatment planning. The proficiency of DL, mainly through DCNN [34], ensures autonomous feature extraction, eliminating manual intervention. This rapid and accurate analysis supports clinicians' decision-making, enhancing diagnostic and treatment processes [35]. Leveraging the analytical abilities inherent in DL algorithms holds promise for elevating disease detection, particularly in oncology. These algorithms excel at decoding intricate patterns within medical datasets, allowing precise identification of minute disease markers. The increased diagnostic accuracy, driven by their adeptness in discerning intricate patterns, significantly improves the detection of diverse cancers.

A study by [36] highlights that integrating three-dimensional holographic microscopy images with DL improves accuracy by capturing comprehensive volumetric information. This aids DL models in precisely identifying 'cancerous' and 'non-cancerous' images, thereby reducing occlusion effects by capturing multiple viewpoints. Figure 5 illustrates the concept of integrating holography microscopic imaging with DL, showcasing how this fusion can enhance disease diagnosis capabilities. HOLOSCOPEi [37], the inaugural holographic system designed for real-time medical applications, distinguishes itself by eradicating the need for head-mounted devices, ensuring user comfort during prolonged usage. Equipped with an advanced 3D visualization tool, it creates tangible organ holograms using CT scans or real-time ultrasound data. This innovative technology enables in-depth exploration of a patient's three-dimensional anatomy, particularly beneficial in procedures like catheter-based valve implantations. Surgeons can virtually interact with holographic structures, contributing to advanced precision. At the end of this section, the following section will outline the complete methodology for integrating holographic imaging and DL to achieve precise cancer diagnosis.

5. Methodological approach in integrating holographic imaging and deep learning for cancer diagnosis

The methodological approach for the collaborative approach of cancer study utilizing DL and holographic images encompasses various systematic strategies including: an extensive literature review covering specific cancer diagnosis, holographic imaging, DL, and their applications. After conducting a comprehensive systematic review, we identified a significant gap in the existing literature. Specifically, prior studies have not fully explored the integration of holographic imaging data with DL algorithms for analyzing complex patterns in various cancer types. Recognizing this gap, the present study aims to shed light on this innovative integration approach's potential benefits and challenges. The primary goal is to enhance diagnostic accuracy in early-stage cancer diagnosis. The critical challenge for this study is to procure a comprehensive dataset encompassing specific cancer-type cases (both 'cancerous' and 'non-cancerous'), along with relevant imaging and clinical information from the collaborating hospital. Ensuring diversity in cases, including different 'subtypes,' 'stages,' and various 'patient demographics' throughout the dataset collection process is essential. This approach aims to cover every possible variation and create a representative and comprehensive dataset for thorough analysis [38].

Following data acquisition, a suitable holography image scanning system will be chosen, considering parameters such as resolution, lighting conditions, and imaging depth to capture high-quality images of tissues collected. The goal is to conduct tissue scanning at the collaborative institute using Digital Holographic Microscope (DHM) capturing light wave phase information and generate high-resolution cell images without staining. The DHM system enables the visualization of cellular structures with precise depth profiling and rich digital imaging of transparent, label-free cells with accurate resolution. DHM captures depth information, including height, by considering quantitative information related to optical paths and the refractive index of tissues. To enable comparative analysis, two-dimensional images of the same tissues must

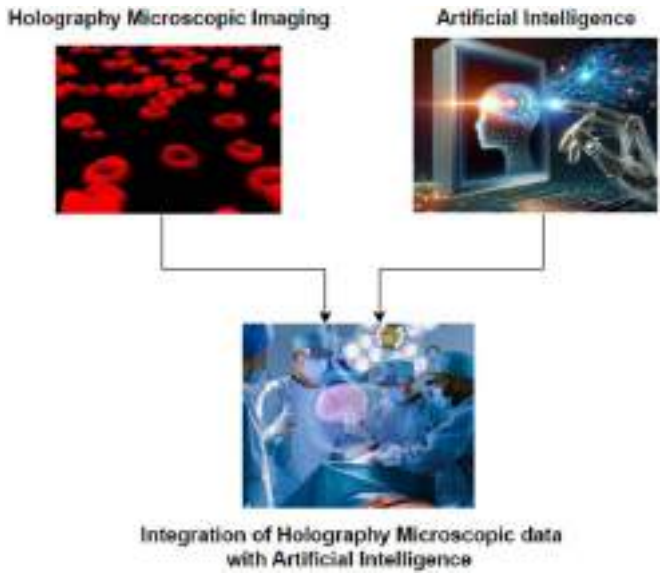

Figure 5. Illustration showcasing holography and DL's potential to revolutionize surgery.

be captured, providing a cross-validation approach to validate the effectiveness of the proposed holographic imaging method. After the thorough scanning of all images in the dataset, the holographic imaging data undergoes preprocessing, including tasks such as 'data balancing,' 'normalization,' 'noise removal,' etc, followed by the feature extraction process [39]. Medical datasets utilized in DL techniques for cancer detection frequently show a noticeable imbalance in class distribution, where the number of 'negative cases (non-cancerous)' significantly outweighs 'positive cases (cancerous).' This imbalance presents a significant challenge for DL models, renowned for their ability to discern intricate data patterns. The potential risk involves a bias towards the more prevalent class, jeopardizing accuracy in cancer detection. Effectively addressing this issue is crucial, as the DL algorithm's performance in identifying cancerous regions relies on its ability to learn from diverse medical data. To address class imbalances, DL methods employ techniques such as the Synthetic Minority Over-sampling Technique (SMOTE) [40],' Deep Synthetic Minority Over-sampling Technique (Deep SMOTE), and Adaptive Synthetic Sampling (ADASYN)[41].' These methods aim to enhance model performance by generating synthetic examples of the minority class to balance the dataset and improve classification accuracy.

Upon preparing the dataset, it is divided into training (for data training), validation (for parameter tuning), and test sets (for assessing the model's performance). Subsequently, a suitable DL architecture/model is selected or designed for analysis. DL architectures such as CNN and Attention-based mechanisms like U-Net attention [42] and ViTs [43] are aimed at determining the dataset's performance. Performance evaluation of the selected or developed DL model involves metrics such as 'accuracy,' 'precision,' 'recall,' 'F1-score,' and 'Area Under the Curve (AUC)' score. To further validate the study, a comparative analysis of the model's performance must be conducted using the corresponding bright-field images of the collected samples. This analysis will help in evaluating the accuracy and reliability of holographic imaging techniques in comparison to conventional imaging methods. Furthermore, the collaborative validation of research findings requires engagement with essential healthcare professionals and experts, including 'radiologists,' 'oncologists,' and other specialists. Additionally, it is crucial to adhere to ethical guidelines addressing concerns such as 'patient privacy,' 'informed consent,' and other privacy issues. Figure 6 illustrates the methodology for analyzing holographic images using DL models, showcasing the sequential steps involved in the process.

While DL algorithms prove to be highly effective, their inherent opacity often leaves healthcare professionals needing clarification about the rationale behind their predictions. This lack of transparency makes it challenging to understand the algorithm, hindering doctors from deciphering the complex factors that influence its results. To address this issue, use of XAI methods [44] such as Gradient-Weighted Class Activation Mapping (Grad-CAM) and Grad CAM++helps in providing valuable insights to doctors by elucidating the decision-making process of specific DL algorithms, particularly in medical context [45]. These techniques operate on visual data, such as images, generating heat maps and highlighting particular areas influencing the algorithm's predictions by analyzing its feature maps. For example, in cancer detection, a DL model may predict the presence of 'cancerous cells' in an image, with Grad-CAM and Grad-CAM++ creating heatmaps overlaid on the original image to reveal the regions where the model focused its

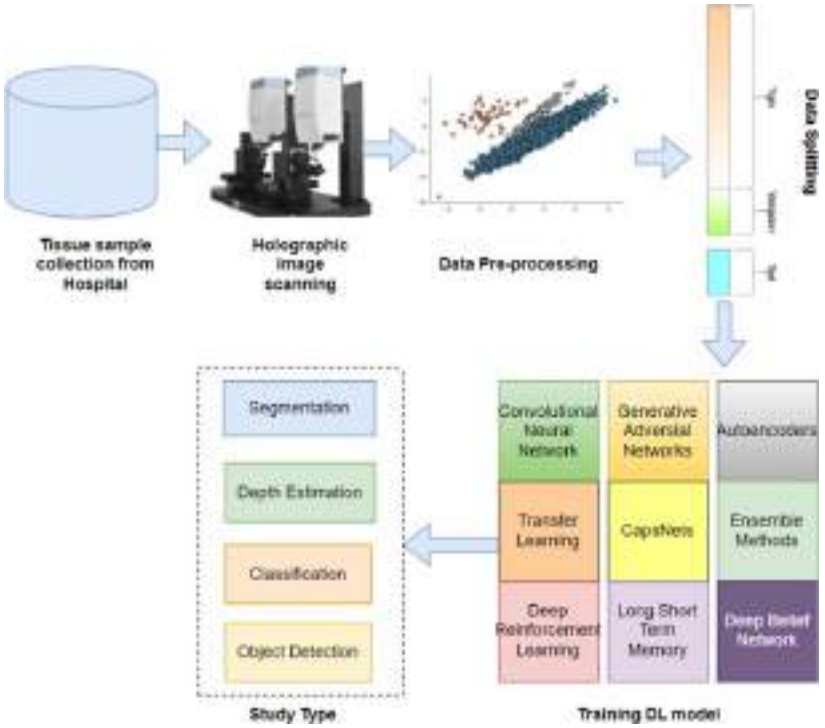

Figure 6. Methodology forholographic image analysis using DL models.

attention during decision-making. This visual representation allows medical professionals to understand the image characteristics that guided the algorithm to a specific conclusion. Healthcare professionals can scrutinize these highlighted areas to validate the alignment between the model's analysis and their medical expertise, ensuring that incorporating XAI in cancer detection during model evaluation aligns AI insights with medical knowledge thereby selecting the best model based on accuracy and interpretability criteria. This promotes informed decision-making and enhances confidence in employing AI for patient care. In the next section of this paper, an elaboration on the diverse benefits associated with integrating holographic imaging and DL for disease diagnosis is provided.

6. Benefits of integrating deep learning and holography microscopic imaging in cancer diagnosis

DL stands out as a powerful tool in cancer diagnosis, utilizing sophisticated algorithms like CNNs, RNNs, and attention-based models. These algorithms meticulously analyze complex medical data, revealing subtle patterns indicative of various cancers. This transformative approach is efficient in the early detection and precise classification of malignancies, like breast and lung cancers. The use of DL algorithms not only enhances diagnostic accuracy but also significantly advances modern cancer diagnosis. The conjunction of holographic imaging and DL yields several advantages, discussed as follows:-

- **Detailed anatomy of biological structures** The fusion of holography microscopic imaging, specifically designed for QPI, marks a revolutionary stride in diagnostics [46]. This advanced imaging technique, meticulously capturing three-dimensional, high-resolution images, goes beyond the conventional techniques. It explores the thickness, height, and intricate details, offering quantitative data via detailed phase maps and intensity profiles. Further, this approach, free from staining requirements, empowers the visualization of cancerous cellular structures with unparalleled precision. It introduces a revolutionary dimension, enabling a deeper and more quantitative understanding of cancer pathology for precise estimations.
- **Enhanced diagnostic speed** DL algorithms demonstrate proficiency in efficiently managing extensively volumetric datasets derived from cell imaging. This integration allows swift analysis and comprehension of microscopic cell images, promoting timely diagnosis and treatment planning [47].
- **Automated analysis** Integrating DL algorithms with holography imaging revolutionizes cancer diagnosis by providing automated image analysis capabilities. Utilizing the extensive three-dimensional information provided by holography imaging, DL algorithms undergo meticulous training to distinguish and categorize diverse cancer cell types,

relying on their distinct holographic attributes. This advanced methodology reduces the need for human involvement in the analysis process, ensuring consistency and efficiency. As a result, diagnostic procedures are optimized, facilitating prompt and precise identification of malignant cells [48].

- **Personalized medicine** Doctors can use advanced DL technology to analyze detailed images of cancer cells captured through holography. This analysis helps doctors understand the specific characteristics of each patient's cancer at a molecular and cellular level. With this knowledge, doctors can customize treatment plans to target the unique features of the cancer cells. This personalized approach leads to more effective treatments, resulting in better patient outcomes [49].
- **Early detection** Detecting cancer early through integrating holography and DL offers substantial benefits for society. By combining these technologies, healthcare professionals can identify cancerous cells at a microscopic level, allowing prompt intervention and improving patient prognosis. Identifying cancer at its earliest stages can prevent its spread within communities, thereby significantly contributing to overall public health. Early detection of cancer not only improves individual health outcomes but also plays a vital role in preventing deaths and saving lives by allowing timely intervention and effective treatment [50].
- **Novel research avenues** Through the fusion of DL and holography imaging, comprehensive insights into intensity and phase details surpass conventional techniques, unlocking avenues for cutting-edge cancer diagnosis. Researchers can explore intricate cellular structures by utilizing DL algorithms alongside holography imaging, paving the path for innovative diagnostic tools and therapeutic approaches on the cutting edge of scientific inquiry. Moreover, based on the existing literature, several types of cancer have yet to be explored for diagnosis using the integrative approach of holography and DL algorithms, presenting a promising opportunity for further research in improving diagnostic accuracy and early detection [51].
- **Interdisciplinary collaboration** Incorporating DL and holography microscopic imaging in cancer diagnosis facilitates interdisciplinary collaboration among 'computer science,' 'biomedical engineering,' and 'physics experts.' This collaboration encourages the exchange of knowledge and ideas, utilizing expertise from various disciplines to advance cancer diagnostics. DL specialists contribute their knowledge in algorithm development and optimization for image analysis. Holography imaging experts offer insights into the distinct features and challenges of using holographic imaging for cancer diagnosis. Oncologists bring their clinical experience and understanding of cancer pathology, ensuring that the technological advancements are effectively translated into practical diagnostic tools. This collaborative approach holds promise in diagnostic abilities, fostering a culture of learning and innovation, with professionals from diverse domains contributing their perspectives to develop innovative diagnostic approaches [52].
- **Enhanced decision-making in cancer diagnosis** A transparent and interpretable decision-making process is ensured by integrating XAI methodologies, such as Grad CAM and Grad CAM ++ [53] analysis, along with advanced techniques like ViTs. This transparency is essential for building confidence in diagnostic procedures and gaining acceptance in clinical settings. The interdisciplinary synergy across physics, medical imaging, computer vision, and AI emphasizes a comprehensive and inventive strategy. This collaboration pushes progress in cancer diagnosis, establishing holography, DL, and state-of-the-art technologies like ViTs, Grad CAM analysis, and Attention-based models (such as U-Net) as fundamental components in developing accurate diagnostic tools for targeted treatment approaches in clinical applications.

The next section gives detailed discussion on use of various XAI techniques and their significance in disease diagnosis.

7. Explainable AI and its impact on clinical decision-making in cancer diagnosis using holographic imaging

The integration of AI in cancer diagnosis offers great potential, but its 'black-box' nature can limit clinical adoption [54]. XAI techniques, such as Grad-CAM [45], Grad-CAM++ [53], and SHapley Additive exPlanations (SHAP) [55], provide transparency, ensuring that AI models focus on clinically relevant features of medical images. When combined with high-resolution holographic imaging, XAI techniques increase confidence in decisions made by DL models [56]. XAI bridges the gap between complex algorithms and human understanding, allowing healthcare professionals to grasp the reasoning behind AI predictions. In critical areas like cancer diagnosis, where errors can be life-threatening, XAI establishes AI as a trusted tool by providing clear, interpretable justifications for clinical decisions. It highlights key regions the model focuses on, enabling doctors to make more informed and accurate diagnoses. The next subsection discusses various XAI methods that are essential for cancer diagnosis.

7.1. Explainable AI methods for cancer diagnosis: Grad-CAM, Grad-CAM++, and SHAP

Among the various XAI methods, Grad-CAM, Grad-CAM++, and SHAP are particularly useful for medical image analysis thereby highlighting the specific regions in images that drive AI-based diagnosis and decisions.

7.1.1. Grad-CAM

Grad-CAM is an XAI method that visualizes the regions of an image that influence a DL model's decision. It calculates the gradients of the target class with respect to the feature maps of the final convolutional layer, which are then used to generate a heatmap. This heatmap highlights the most important areas of the image that contributed to the model's prediction, providing transparency into the model's decision-making process. Grad-CAM is particularly valuable in fields like medical image analysis, where it helps clinicians better understand and trust AI-driven results. Grad-CAM visualizes CNN decision-making by computing the predicted class score for the target class and the gradients of this score with respect to the activations in the final convolutional layer [45]. These gradients are averaged across spatial locations to obtain a weight for each feature map. The weighted sum of these feature maps is then calculated, followed by a Rectified Linear Unit (ReLU) activation to focus on positive contributions. The final heatmap is generated by resizing the result to match the original image, highlighting the regions that influence the classification decision. This approach improves model interpretability, especially for complex tasks like medical image analysis.

A study by [57] demonstrated that CNNs accurately detect head and neck cancer in histopathological slides, achieving 89.9% accuracy on unseen data. Using XAI techniques like Grad-CAM and HR-CAM, the networks focused on nuclear features of atypical cells, aligning with pathologists' analysis. Their results suggest that CNNs, when paired with visual explanations, can assist pathologists in cancer diagnosis. Further validation with XAI methods like Deep Learning Important FeaTures (DeepLIFT) could improve the findings. A novel mammogram image-based BCaXAI model, proposed by [58], utilizes the Inception-ResNet V2 architecture and incorporates Grad-CAM for enhanced explainability, aiming to provide accurate, noninvasive, and timely breast cancer diagnosis.

7.1.2. Grad-CAM++

Grad-CAM++ enhances the original Grad-CAM by incorporating higher-order derivatives to improve the accuracy of feature map weighting [53]. Unlike Grad-CAM, which uses first-order gradients of the class score with respect to the feature maps, Grad-CAM++ integrates second and third-order derivatives, allowing for a more refined understanding of feature map contributions. This modification helps Grad-CAM++ better capture complex features, specifically when objects vary in angle or partial visibility, by focusing on positive gradients that highlight object presence. By incorporating higher-order gradients, Grad-CAM++ reduces the influence of suppressive gradients, leading to more precise and clearer visualizations of the model's decision-making process, particularly in cancer diagnosis. This enhancement enables better identification of features crucial for cancer diagnosis, leading to more accurate and interpretable model predictions. It clarifies the factors influencing the model's output, ensuring more reliable results for cancer detection. A study by [59] presented a DL model for skin cancer classification that addresses class imbalance and integrates interpretability using Grad-CAM and Grad-CAM++. The model proposed, optimized with Adam and RMSprop on the HAM10000 dataset, achieved 82% accuracy, with Grad-CAM++ providing essential visual insights for early, accurate skin cancer diagnosis. The study by [60] targets lung cancer detection using an advanced approach that integrates Grad-CAM++ with a 3D CNN to help classify lung nodules and support early diagnosis. Grad-CAM++ improves model interpretability by visualizing decision pathways, assisting radiologists build trust in its diagnostic use.

7.1.3. SHAP

SHAP helps make DL model predictions easier to understand by showing how much each feature contributes to the outcome, balancing both accuracy and interpretability [55]. The study by [61] presents a lung cancer classification model that combines Lightweight Parallel Depth-wise Separable Convolutional Neural Network (LPDCNN) with Ridge Regression Extreme Learning Machine (Ridge-ELM) for CT image analysis. Additionally, SHAP (Shapley Additive Explanations) is integrated into the model to improve its explainability, providing insights into the decision-making process. In [62], XAI is used to predict successful surgical cytoreduction (R0 resection) in Epithelial Ovarian Cancer (EOC) patients. Their study uses an XGBoost model with SHAP explanations to pinpoint key patient and surgical factors, boosting accuracy in predicting R0 resection results for epithelial ovarian cancer. Their approach improves surgical planning and strengthens quality control in patient care.

7.2. Incorporation of Explainable AI with holographic imaging data

A literature review underscores how XAI fosters trust in DL models by offering transparency, allowing healthcare professionals to understand AI decisions and confidently apply AI-driven insights. Building on this, we propose that the integration of XAI with three-dimensional holographic imaging data has the potential to significantly improve diagnostic accuracy and

decision-making processes in healthcare. By providing both interpretability and rich visual data, this combination could enhance the trust and understanding that medical professionals place in AI-driven diagnostic systems. This future approach aims to not only improve the accuracy of diagnosis but also offer greater interpretability, thus providing clinicians with confidence in using complex holographic data for decision-making. In their study, [63] applied Grad-CAM to visualize focus areas of CNN models during training. They found that DenseNet169 targets specific regions within the hologram, enhancing model interpretability. In their study, [64] utilized Grad-CAM, CAM, and Guided Back Propagation (Guided BP) to visualize the decision-making regions in deep networks. These techniques were applied to holographic images of both clean and noisy specimens. Grad-CAM pinpointed critical regions for model predictions, improving diagnostic accuracy by detecting target objects, noise, and image defects, thereby improving interpretability. This review study reveals that there is limited research on the use of XAI in cancer diagnosis through DL models applied to holographic images, highlighting this as a promising area for future investigation. The next section of this paper explores strategies to overcome dataset limitations, focusing on synthetic data generation, transfer learning, and other techniques.

8. Strategies to overcome dataset limitations: synthetic data generation, transfer learning, and other techniques

In cases where data scarcity is a concern, addressing dataset limitations becomes significant for building DL models that are both robust and generalizable, particularly in domains with imbalanced data. This section investigates key strategies to mitigate these issues, including synthetic data generation, transfer learning, and other similar techniques.

8.1. Synthetic data generation

Synthetic data generation can prove a powerful tool to overcome limitations associated with small, imbalanced datasets [65]. This method ensures diversity and balance within training datasets by creating realistic artificially generated medical images. Techniques such as GANs and Variational Autoencoders (VAEs) are effective solutions to address data scarcity problems. A study by [66] highlights key challenges in cancer detection, such as data scarcity and tumor heterogeneity, which impact diagnosis accuracy. GANs are presented as a promising solution, generating synthetic images to augment limited datasets and simulate various cancer types. Their review examines 163 papers on GANs in cancer imaging, highlighting their techniques, benefits, and limitations, while proposing future research to align AI advancements with clinical needs. The study by [67] addresses the issue of limited annotated data in medical imaging by proposing a Self-Supervised Learning (SSL) model. Their model uses VAEs to effectively leverage unlabeled data, learning discriminative features through a pretext task. By using the limited labeled data effectively, this approach helps to overcome data scarcity, improving the accuracy of mammography classification even with fewer labeled samples.

8.2. Transfer learning

Transfer learning provides an effective strategy for overcoming limitations in datasets by utilizing pre-trained models, allowing for improved performance even with smaller data. Pre-trained models are ML models trained on large and diverse datasets, such as ImageNet for image classification, COCO for object detection, and GLUE for natural language understanding tasks. Pre-trained models, which have already learned patterns from large datasets, can be adjusted and fine-tuned to work better on smaller, specific datasets, improving their performance for particular tasks. AlexNet, introduced in 2012, is one of the earliest and most influential transfer learning models, known for its success in large-scale image classification tasks [68]. Some other popular models for transfer learning include VGG16 (Visual Geometry Group) [69], ResNet (Residual Network) [70], etc,. These models, initially trained on large datasets like ImageNet, offer a solid foundation for specialized applications with minimal data. A comprehensive discussion of transfer learning in various studies is presented in subsection 9.3 of section 9.

8.3. Class imbalance handling techniques

Class imbalance is a common challenge in small and scarce datasets, particularly in domains like medical imaging, where abnormal cases are underrepresented. Addressing this imbalance is essential for building DL models that are both robust and generalizable. This section focuses on resampling and ensemble techniques that can be used to effectively handle class imbalance.

8.3.1 Resampling techniques

These techniques help balance datasets by increasing the instances of the minority class or decreasing the instances of the majority class to address class imbalance effectively.

Under-sampling techniques

These techniques involve reducing the number of samples from the majority class to balance the class distribution in a dataset. Common methods include random under-sampling, NearMiss (which selects majority class samples based on their proximity to the minority class), and Tomek Links, which removes majority class samples that are closest to the decision boundary.

Random under-sampling. Random under-sampling is a technique used to balance imbalanced datasets by reducing the number of samples from the majority class. In this method, a subset of the majority class is randomly selected and retained, while the remaining samples are discarded. This helps to balance the class distribution and prevents the model from being biased towards the majority class. While it can improve the model's performance on minority class prediction, it may also lead to a loss of valuable information, especially if the dataset is small.

Near miss. NearMiss is an under-sampling technique that selects majority class samples based on their proximity to minority class samples. It helps balance the dataset by keeping the majority class instances closest to the decision boundary. There are different versions, such as NearMiss-1, NearMiss-2, and NearMiss-3, which vary in selection criteria, aiming to improve model performance by preserving informative majority class samples.

Oversampling techniques

Oversampling techniques improve the minority class representation by creating new samples or duplicating existing ones, helping to balance the dataset. The following are various techniques used for balancing datasets through oversampling:

SMOTE (Synthetic Minority Oversampling Technique). SMOTE addresses class imbalance by generating synthetic data for the minority class. It starts by identifying minority class samples and selecting their closest neighbors using a distance metric [71]. A random proportion of the difference between the minority instance and its neighbor is then added to the original instance to generate a synthetic data point. This process is repeated until the desired number of synthetic samples is generated. SMOTE helps prevent overfitting by introducing diversity in the minority class and enhances decision boundaries, rather than just replicating existing data.

Borderline SMOTE. Borderline SMOTE is an extension of the SMOTE algorithm that focuses on minority class samples near the decision boundary between classes [72]. These borderline instances are usually harder to classify and are often misclassified. Borderline SMOTE generates synthetic samples to address this by selecting the nearest neighbors of borderline instances thereby creating new data points. This is achieved by adding a random proportion of the vector difference between the instance and its nearest neighbor to the original instance. This strategy targets difficult-to-classify regions, optimizing decision boundaries and enhancing the classifier's performance on imbalanced datasets.

Deep SMOTE. Deep SMOTE generates synthetic data for the minority class by leveraging a three-component framework [73]. First, it uses an encoder-decoder structure to learn compact, informative representations of minority class samples. Next, it applies the traditional SMOTE method to generate synthetic instances by interpolating between the minority samples and their closest neighbors. This process generates new data points that resemble the original instances but introduce slight variations, ensuring they are not exact replicas. Further, it incorporates a custom loss function enhanced with a penalty term to ensure the quality of generated samples. Unlike GAN-based approach, Deep SMOTE simplifies the process by not requiring a discriminator, while still generating high-quality synthetic samples.

ADASYN (Adaptive Synthetic Sampling). ADASYN adapts the process of oversampling by targeting minority class instances that are difficult to classify, particularly those near the decision boundary [74]. The key idea is to evaluate the learning difficulty of each minority sample based on the density of its neighboring minority points. Instances that are more difficult to classify, typically due to their isolation from other minority class points, are assigned a higher number of synthetic samples to enhance their representation. ADASYN adaptively shifts the decision boundary by increasing the representation of challenging instances, improving model performance. This technique leads to more balanced training data, resulting in improved model robustness.

8.3.2 Ensembling techniques

Bagging and boosting are ensemble learning techniques, but on their own, they are not specifically designed to handle class imbalance. However, they can be adapted to improve model performance on imbalanced datasets.

Bagging

Bagging (Bootstrap Aggregating) improves model performance by generating multiple versions of a predictor and aggregating them to form a better classifier [75]. It makes bootstrap replicates by sampling from the original dataset, training separate models on each, and then merging their predictions using majority voting for classification. To tackle class imbalance, bagging can be adjusted by either increasing the number of minority class instances or reducing the number of majority class instances within each bootstrap sample. Bagging addresses class imbalance by creating multiple models with bootstrapped datasets that balance class representation through oversampling or undersampling. It improves the accuracy of minority class predictions while stabilizing results for unstable classifiers, improving overall classification performance.

Boosting

Boosting can be adapted for handling class imbalance by adjusting how weights are assigned to instances during the training phase [76]. In algorithms like AdaBoost, higher weights can be assigned to samples from the minority class, prioritizing them during the training process to ensure better representation. Boosting can be combined with resampling strategies like oversampling the minority class or undersampling the majority class to achieve a more balanced dataset,

and enhance the model's performance on imbalanced data. Boosting improves model performance on imbalanced datasets by iteratively refining weak classifiers to target misclassified instances. This process strengthens the representation of the minority class, addressing classification errors and improving the overall predictive accuracy.

8.3.3 Other Techniques

Other techniques like, Few-Shot Learning (FSL) tackles the challenge of training models with few examples by helping them generalize effectively from a small dataset [77]. FSL addresses the challenge of training models with minimal labeled data by employing meta-learning, metric-based methods, episodic training, and leveraging data augmentation techniques to improve generalization. Meta-learning involves training models to quickly adapt to new tasks by learning from multiple tasks [77]. One prominent example is Model-Agnostic Meta-Learning (MAML), which aims to optimize model parameters so they can be fine-tuned with minimal adjustments for new tasks. This enables the model to perform effectively with only a few examples, thus reducing the reliance on large, task-specific datasets. Metric learning methods like 'Prototypical Networks' classify by comparing new samples to class prototypes in feature space, while 'Siamese Networks' assess the similarity between pairs of data to determine if they belong to the same class [78]. Episodic training in few-shot learning involves simulating tasks with limited labeled support sets and query sets, enabling the model to generalize across diverse tasks with small data [79]. External knowledge sources, such as pre-trained embeddings and data augmentation strategies, can be utilized to enhance model robustness and increase data diversity.

8.4. Data augmentation techniques

Data augmentation plays a significant role in boosting the performance of ML models, particularly when faced with imbalanced or limited labeled datasets [80]. By generating synthetic variations through transformations like 'rotation', 'scaling', and 'flipping', it allows models to generalize better. This is particularly beneficial for tasks like object detection and semantic segmentation, where the variety in training samples directly impacts the model's learning capacity. In addition to conventional data augmentation methods like 'rotation,' 'scaling,' and 'flipping,' more progressive techniques have emerged that significantly improve model performance by creating more diverse and challenging training examples. Among these strategies are 'CutMix,' 'MixUp,' and 'Cutout,' which offer novel ways to regularize training and improve generalization.

8.4.1 CutMix

CutMix is a data augmentation strategy that generates new training images by extracting a rectangular section from one image and placing it onto another [81]. The new label is derived as a weighted blend of the original labels, with the weight proportional to the area of the inserted region. This approach helps the model to focus on incomplete or occluded features, enhancing its ability to generalize effectively to new and unseen data. CutMix enhances model robustness by blending spatial and label data during training, which helps to regularize the learning process thereby reducing overfitting. This approach allows the model to handle challenges such as partial occlusions and noisy data more effectively, leading to better generalization in real-world scenarios.

8.4.2 MixUp

MixUp is a data augmentation method that creates synthetic training samples by blending input images and their associated labels via linear interpolation [82]. Two images are merged to create a new mixed image, and the labels are also interpolated using the same ratio. This approach enables the model to learn smoother decision boundaries, improving its ability to generalize effectively while reducing the risk of overfitting. In medical imaging, where dataset instances are often limited, MixUp helps the model focus on broader features, making it useful for tasks like tumor detection and segmentation. It is crucial to ensure that mixed images maintain clinical relevance and realism, as the process may sometimes produce intermediate samples that are not easily interpretable or accurate in a medical context.

8.4.3 CutOut

CutOut is a data augmentation technique that improves model generalization by randomly masking parts of an image, prompting the model to target the remaining visible features [83]. By masking parts of an image, the model learns to focus on visible features, improving its robustness to occlusions and missing sections. This technique helps the model focus on broader patterns, which enhances its ability to handle real-world challenges where data may be incomplete or partially hidden. A random portion of the selected image is masked (10-50% of the image), replacing its pixels with a constant value like zero, forcing the model to focus on the remaining visible areas and reducing overfitting. The application of multiple masks helps the model focus on a broader range of features, improving its ability to learn diverse patterns. After reviewing the various strategies to handle limited dataset, the following section provides an in-depth discussion of various studies demonstrating the integration of holographic imaging and AI techniques, such as ML and DL, for cancer and other cell imaging procedures.

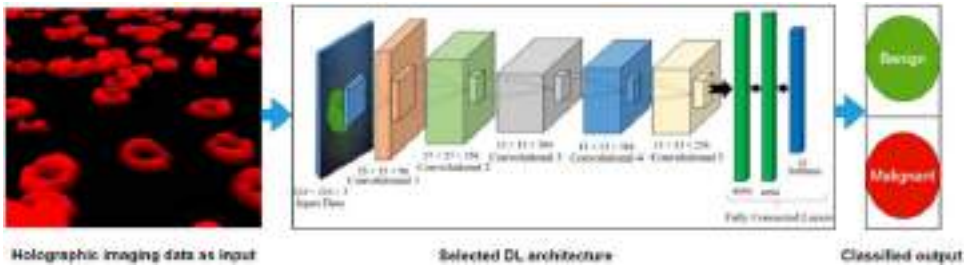

Figure 7. Generalized framework for analyzing and processing holographic images.

9. Artificial intelligence and holography microscopic imaging in disease diagnosis

Cancer is a major global threat, characterized by the uncontrolled growth of abnormal cells, and is a leading cause of death worldwide. In 2023, the United States is expected to report 1.96 million new cancer diagnoses and 609,820 deaths, emphasizing the urgent need for ongoing improvements in medical treatments and interventions. Despite progress, challenges remain, as rising cancer incidence rates and significant racial disparities in mortality highlight the need for continued efforts to address complex cancer forms [84]. Early detection of cancer is crucial for improving treatment results, yet identifying it at an early stage presents numerous challenges. Global cancer statistics highlight the need for more advanced diagnostic techniques across various types. Timely diagnosis enables more effective treatments, leading to improved healthcare outcomes. Prostate cancer, a prevalent global malignancy, develops in the prostate gland and is more common among older men, with an increased risk observed in those over 65. Cancer prevalence varies based on regional and demographic factors. Prostate cancer incidence increased by 3% annually from 2014 to 2019, resulting in 99,000 new cases. Conversely, lung cancer rates declined, with women experiencing a slower decrease (1.1% annually) compared to men (2.6% annually) from 2015 to 2019. Breast and uterine corpus cancers are prevalent among women, posing increasing challenges. However, a positive trend is observed in cervical cancer incidence, with a substantial 65% decline from 2012 to 2019 among women in their early 20s related to the introduction of the Human PapillomaVirus (HPV) vaccine. This underscores the effectiveness of targeted preventive measures and emphasizes the dynamic nature of women's cancer prevalence.[3]

With the advancement of AI in healthcare, especially in medical imaging, algorithms like CNNs, RNNs, and transformers (e.g., U-Net and ViT) are reshaping diagnostic processes. These techniques leverage large datasets to detect complex patterns in medical images, enhancing diagnostic accuracy. In this section, we thoroughly examine the integration of holographic microscopic imaging with AI techniques, including ML and DL, for cancer diagnosis. The studies are categorized according to the specific AI methods applied for early disease detection. Figure 7 presents a generalized approach for analyzing holographic data utilizing DL models.

9.1. Machine learning and holography for disease diagnosis

This subsection delves into examining different studies that integrate ML and holography for disease diagnosis. A study by [85] addressed the detection of Circulating Tumor Cells (CTCs) in cancer patients' blood samples. The authors propose a staining-free approach for CTC count using DHM, microfluidics, and ML. Using holographic in-focus images, they developed S-Net, a custom shallow network for tumor cell classification in blood samples. S-Net surpassed ResNet-50 [86], showcasing higher accuracy, sensitivity, and specificity with shorter training times, and successfully reduced false positives in mixed samples using an optimized threshold. This study addresses the limitation of immunostaining for live CTC access, achieving successful tumor cell enumeration in lysed blood samples and paving the way for a stain-free method to count actual CTCs in cancer patients. The potential challenges include the development of universal markers acquiring real-world data for ML, with the translation to patient samples still being explored. [87] use digital holographic microscopy to organize cervical cells autonomously, highlighting enhanced clustering with brightfield and QPI. Employing Principal Component Analysis (PCA) [88], their study demonstrates improved clustering and emphasizes the valuable contribution of non-redundant phase information for automated cell classification. The authors highlight the valuable contribution of non-redundant phase information for automated cell classification and propose potential tool development for assisting pathologists. However, concerns arise from a small sample size (10 women), impacting generalizability, limited applicability beyond cervical cells, and a lack of real-world clinical performance data.

[3] https://seer.cancer.gov/statfacts/, https://www.cancer.org/research/cancer-facts-statistics.html

[89] present an automated diagnostic system utilizing QPI and ML for Gleason grading of prostate specimens. Using interferometry, the system exposes intricate nanoscale architectural features in unlabeled specimens. The random forest classifier [90] is trained to identify textural behaviors, and logistic regression combined morphological features with quantitative data, achieving an accuracy of 82% in distinguishing between Gleason grade 3 and grade 4 cancer in prostatectomy tissue. Their study acknowledges limitations, including reliance on a dataset of 288 cores from a tissue microarray, possibly not fully capturing prostate cancer sample variability. Additionally, the study needs more discussion on computational intricacies and efficiency, vital for practical implementation in clinical settings. [91] introduced a stain-free technique for automatically classifying live cancer cells using ML and QPI. By analyzing spatial fluctuations in cell phase, indicative of stiffness and metastatic potential, the technique employs holographic imaging for quantitative profiling during flow. SVMs [92] are utilized for cancer and blood cell classification, achieving an accuracy of 92.56%. While promising for unbiased clinical diagnosis, the study's limitations include a small training set (133 images per cell type) that may impact the DL classifier's performance and restrict generalizability. Moreover, the focus on SW480 and SW620 cells limits direct applicability to other cancer types or cell lines.

[93] introduced a novel method for real-time estimation of cellular viability, leveraging supervised ML and intracellular dynamic activity data obtained in a label-free, non-invasive, and non-destructive manner. Their study attained a balanced accuracy of 93.92 $\pm$ 0.86% in cell death assay performance by utilizing four supervised ML models: SVM, logistic regression [94], gaussian naive bayes [95], and random forest. Random forest emerges with the highest classification accuracy, reaching 95% on the test dataset. Their strategy differs from traditional staining approaches, clarifying the criteria for assessing cell viability. These findings have implications for diverse fields requiring cellular analysis and are poised to advance medical research significantly. [96] introduced a novel method for diagnosing sickle cell disease by analyzing spatio-temporal cell dynamics using 3D printed shearing digital holographic microscopy. Researchers utilized a low-cost, compact interferometer to capture video holograms of healthy and diseased Red Blood Cells (RBCs). After capturing a video hologram using the portable DHM setup, cells within human blood smears, including healthy RBCs (h-RBC) and those with Sickle Cell Disease (SCD-RBC), are manually segmented. Subsequently, a 3D reconstruction of each cell's optical path length profile across all frames is generated, enabling the estimation of dynamic fluctuations through optical flow analysis. Spatial features obtained from these profiles, alongside various morphological cell parameters like mean optical path length, coefficient of variation, and optical volume, are leveraged to bolster classification accuracy. A random forest classifier underwent training for cell identification, distinguishing between SCD-RBCs and h-RBCs with outstanding accuracy. Their experimental setup comprised three training sets: the first containing solely spatio-temporal features, the second consisting solely of morphological features, and the third integrating both features. The combined approach achieved 100% accuracy in detecting both SCD-RBC and h-RBC.

[97] implemented and validated ML classifiers capable of distinguishing between cell states and cell lines, specifically HeLa (Cervical Cancer cell lines), A549 (lung carcinoma epithelial cell lines), and 3T3 (mouse embryonic fibroblast cell lines). They developed a classifier demonstrating an accuracy of approximately 93% for differentiating between the three cell types and about 89% for distinguishing between various cell states within the same cell line. Furthermore, after photodynamic treatment at different doses, the algorithm successfully evaluated the temporal dynamics of relative amounts of live, apoptotic, and necrotic cells. [98] introduced an AI-based holographic imaging method for differential screening of anemia patients. Their study demonstrates the application of hierarchical ML on a limited dataset for comprehensive clinical screening. Utilizing holography imaging combined with ML, they developed a differential classifier capable of distinguishing between normal RBCs and various hereditary anemias, including Iron Refractory Iron Deficiency Anemia (IRIDA), α-thalassemia, Hereditary Spherocytosis (HS), Congenital Dyserythropoietic Anemia (CDA's), and Dehydrated Hereditary Stomatocytosis (DHS1). Their classifier utilized 16 customized characteristics to train two SVM classifiers, with the second one activated for diseased samples. Their approach achieved 84.3% accuracy in the binary pre-screening stage and between 51.2% and 83.9% in identifying different types of anemia, with IRIDA and CDA-I identification having the highest and lowest accuracies, respectively.

[99] proposed two distinct ML methodologies for cell classification based on label-free QPI utilizing transport of intensity equation techniques. The first method employs a multilevel integrated classifier comprising diverse individual models such as Artificial Neural Networks (ANNs) [100], extreme learning machines, and generalized logistic regression. The second method utilizes a pre-trained CNN with transfer learning. Both approaches demonstrate high accuracy, with the multilevel integrated classifier achieving an average accuracy of 93.1%, comparable to CNN's 93.5%. The proposed QPI system, merged with these classification techniques, presented a valuable tool for biomedical scientists, offering convenient and precise cell analysis abilities. Table 1 presents a compilation of studies integrating ML and holography for disease diagnosis.

Table 1. Machine learning and holography for disease diagnosis.

Reference of paper	Integration Type (Disease type + Imaging technique type + Kind of AI technique)	Dataset	Evaluation Metric
[85], Gangadhar *et al* 2023	Breast cancer (MCF-7) and ovarian cancer (SkOV3) + Holography microscopy + S-Net (a custom-designed light-weight shallow network)	In-house Dataset	Confusion matrices, Accuracy (98.25), Sensitivity (97.62), and Specificity (98.89)
[89], Nguyen *et al* 2017	Prostrate cancer + QPI + Random forest classifier and Logistic regression	Not Available	Accuracy (82%), Coefficient of Variation and Fusing Ratio
[91], Rotman-Nativ and Shaked, 2021	SW480 cells, Colorectal adenocarcinoma cells from colon tissue, and SW620 cells, metastatic cells from a lymph node of the same donor's colon, were studied + VGG16	Data not available publicly	Accuracy (92.5%), Sensitivity: (88.88%) , Specificity (96.25%), and AUC (0.961%)
[87], Mangal *et al* 2018	Cervical cancer + Holography microscopic imaging + Unsupervised learning	Data may get available upon request	PCA methodology is used to evaluate the clustering performance
[93], Park *et al* 2022	HeLa cells + Dynamic Full-Field Optical Coherence Microscopy + Four supervised ML models are applied to the observed data: Logistic Regression, Random Forest, SVM, and Gaussian Naive Bayes classifiers	Data available on request	Sensitivity (97.89 ± 0.67%)->Live cells, Specificity (90.28 ± 2.34%)->Dead cells and Balanced Accuracy (93.92 ± 0.86%)
[96], Javidi *et al* 2018	Sickle cell disease + Digital holographic imaging + Random Forest Classifier	Data not available publicly	Accuracy (93.33%) , Specificity (100%) and Accuracy (86.67%)
[97]. Belashov *et al* 2021	Cell types (HeLa, A549, 3T3 cell lines) and States (live, necrosis, apoptosis) + QPI + SVM, k-NN (k-Nearest Neighbors) and EC (Ensemble Classifier)	Data is not available publicly	Accuracy for distinguishing between different cell types(93%) Accuracy for distinguishing between different cells (89%) Accuracy for distinguishing between cells of different lines and states(77%)
[99], Li *et al* 2020	Macrophages (type of white blood cell) + Quantitative Phase Microscopy with transport of intensity equation + Multilevel integrated classifier and CLSNet with data augmentation	Not available publicly	Accuracy (93.1 ± 2.4 %), AUC (98.5 ± 1.7%) and Computational time (3.4 ± 0)-> For Multilevel integrated classifier
[98], Memmolo *et al* 2022	Anemia + Label-free holographic microscopy + Hierarchical ML technique	Not available publicly	Not mentioned

9.2. Deep learning and holography for disease diagnosis

This subsection examines different studies that combine DL and holography for different disease diagnoses. [101] introduced a Deoxyribo Nucleic Acid (DNA)-focused microphotography platform for rapid point-of-care HPV screening, revealing outstanding sensitivity and specificity. Using a DL approach 120-fold faster than traditional approaches completes analysis very fast. In a blinded clinical study, the platform successfully benchmarks against a Food and Drug Administration (FDA)-approved HPV assay, demonstrating the potential for decentralized testing in underserved populations. Their study employs customized DL algorithms in a microphotography platform for point-of-care HPV screening, utilizing two shared-parameter CNNs. The

networks efficiently count polystyrene, silica, and dimers from diffraction images, exemplifying effectiveness without intensive computations for rapid and accurate point-of-care cervical cancer screening. However, their investigation lacks validation in various contexts and concentrates on specific high-risk HPV strains, neglecting details on cost and scalability. Further, addressing potential challenges in deploying the platform in resource-constrained regions requires attention.

[102] proposed an innovative approach integrating label-free optical assay and whole-genome sequencing to diagnose microbial infections and AntiMicrobial Resistance (AMR) rapidly. The research involves a curated dataset of 472,795 resized bacteria images (224 $\times$ 224), distributed into 80% training, 10% validation, and 10% testing sets. This dataset plays a vital role in training a deep residual learning framework, serving as a standard for performance evaluation. Quantitative phase microscopy and DNNs accurately classify species, gram staining, resistance types, and strain-level details, particularly for World Health Organization (WHO)-priority pathogens. Their approach is a rapid initial tool for efficient antimicrobial stewardship in clinical settings. It utilizes DCNNs for species-level classification, gram staining, resistant/susceptible types, and strain-level classification. [103]'s contribution involves diagnosing lung squamous cell carcinoma using quantitative Transmitted Intensity Differential Interference Contrast (TI-DIC) microscopy and a DCNN . The authors used a DCNN to classify lung squamous cell carcinoma tissue using DIC images or optical property maps. The DCNN, especially with visual property maps, achieved higher accuracy than DIC images. DL, particularly DCNN, has shown promise in tissue imaging and diagnosis, including discriminating cancer and normal tissue sections. Incorporating label-free quantitative phase microscopy with DCNN presented a promising prospect for expeditious and precise cancer diagnosis. Moreover, diverse datasets, including cancer types and stages, are pivotal. Also, cross-validation ensures robust DCNN performance on distinct dataset subsets, while regularization methods, such as dropout, prevent overfitting, improving the model's adaptability to data variability.

[104] addresses cancer cell classification (lung, breast, skin) utilizing stain-free quantitative phase images from digital holography. Using feature-based ML and image-based DL with a CNN, the latter outperforms feature-based classification by around 9% accuracy via 10-fold cross-validation. Their research highlights the superiority of CNN-based DL for cancer cell classification in digital holography microscopy. The proposed model eliminates manual inspection, effectively classifying organ cancer cells with similar morphological structures. However, one of the limitations of this study is the need for more information regarding the dataset size used for training and testing, which can impact the generalizability and robustness of the proposed DL model. [105] introduced a label-free imaging flow cytometry approach operating interferometric projections and using DL for cell classification (including metastatic breast carcinoma cells MCF-7 and normal human mammary epithelial cells MCF-10A). It highlights classifying cells directly from Optical Path Difference (OPD) [106] projections, demonstrating improved accuracy with multiple OPD projections. The late fusion methodology integrates numerous heads of the classification network considering various viewing-angle projections, strengthening the network's ability to determine intricate features. Their study details a comprehensive classification network using a 'Michelson Holographic Interferometer' for imaging white blood and breast cells, using ResNet-18 with skip connections for effective vision tasks. Crucial factors include accurate projection angle estimation and the impact of reliance on sufficient cell training on accuracy. Further research is needed for broader validation and performance evaluation, particularly considering the study's focus on specific cell types without direct comparisons.

[107] presented PhaseStain, a digital staining method utilizing a DNN to transform label-free quantitative phase microscopy images into histologically stained images resembling brightfield microscopy images. This technique demonstrates versatility across various quantitative phase imaging methods, regardless of the specific imaging setup or phase recovery approach. By training a GAN [108] on pairs of image data consisting of holographic images and corresponding brightfield microscopy images, PhaseStain effectively replicates staining effects on human skin, kidney, and liver tissue sections. The elimination of traditional histological staining procedures by PhaseStain potentially leads to cost savings and time efficiency in sample preparation, thereby promoting the adoption of label-free QPI techniques in biomedical research. [109] introduced two models utilizing a Fully Convolutional Neural Network (FCN) algorithm, namely FCN-1 and FCN-2, to extract RBC features from RBCs holographic images. FCN-1 exclusively uses the FCN algorithm for RBC prediction, while FCN-2 integrates the FCN approach with the marker-controlled watershed transform segmentation scheme for RBC extraction. Both models achieve significant segmentation accuracy, with FCN-2 demonstrating superior cell separation compared to conventional methods. RBC phase images are reconstructed numerically from holograms captured via off-axis digital holographic microscopy, and manual segmentation aids in refining the FCN through training data. FCN-1's segmentation result serves as the prediction result for RBCs, while FCN-2's result improves segmentation using the marker-controlled watershed transform algorithm. This combination streamlines RBC extraction and improves separation outcomes.

Table 2. Deep learning and holography for disease diagnosis.

Reference of paper	Integration Type (Disease type + Imaging technique type + Kind of AI technique)	Dataset	Evaluation Metric
[102], Ahmad *et al* 2022	Identification of microbial infections, including bacterial pathogens, in clinical settings + QPI + DCNNs	Publicly Not available	Accuracy (100% for gram-negative, 83.4% for gram-positive, 98.6% for Species, and 96.4% for resistance/susceptibility type, 100% for 19 out of 21 strains)
[103], Zheng *et al* 2019	Lung cancer + Quantitative Differential Interference Contrast Microscopy + DCNN	Not Available Publicly	AUC (%96.8), Accuracy(%95.7)
[104], Jaferzadeh *et al* 2023	Three types of cancer cell lines (lung, breast, and skin) + Digital Holography Microscopy + Two types of CNN models (one with skip connections and another without skip connections)	Data not shared	Accuracy (95%)
[105], Cohen *et al* 2024	Metastatic breast carcinoma cells (MCF-7) and normal human mammary epithelial cells (MCF-10A) + Quantitative Phase Imaging System + ResNet -18	Not Available	Accuracy (98.1% to 99.9%)
[101], Pathania *et al* 2019	Cervical cancer + Microholography + Customized DL algorithm designed	In-house Dataset	Specificity (100%), Accuracy (99% for PS beads, 98% for silica beads, and 82% for dimers) and Correlation
[107], Rivenson *et al* 2019	Skin, kidney, and liver tissue + QPI + GAN	Data not available	Not mentioned
[109], Yi *et al* 2017	RBC Segmentation + Digital holography microscopy + FCNs	Data available on request	Segmentation accuracy for • FCN-1 (95.03%) • FCN-2 (95.57%)
[110], Kima *et al* 2021	Pathogenic bacteria species + 3D QPI + ANN	Dataset is prepared manually	Accuracy (99.99%)

[110] introduced a novel identification framework capable of accurately discerning the species of bacterial bloodstream infection pathogens from a single colony-forming unit, leveraging three-dimensional QPI and ANNs. Attaining an outstanding accuracy of 99.9% in distinguishing among 19 bacterial species when tested with ten bacteria, the framework showcases promise as a valuable aid for clinicians in making initial antibiotic prescription decisions. It underscores the effectiveness of three-dimensional QPI in profiling individual bacterial cells by highlighting the capability of ANNs to extract species-specific features from imaging data. This ability overcomes the volume constraints of previous microbial identification methods. Moreover, the authors foresee the potential of the framework to be relevant for pathogens causing various types of infections and underscore the significance of evaluating its effectiveness in discerning antibiotic-resistant strains to improve its performance. Table 2 provides a comprehensive overview of studies utilizing DL and holography for disease diagnosis.

9.3. Transfer learning and holography for disease diagnosis

This subsection discusses the role of transfer learning in facilitating the efficient training of AI algorithms. Integrating transfer learning [111] with holography, plays a crucial role when dealing with limited data. Transfer learning, leverages pre-trained DL models like VGG [112], ResNet [113], etc, trained on datasets like ImageNet [114], adapted to new datasets with limited labeled data, significantly improving diagnostic accuracy. When combined with holographic data that provides rich and detailed insights, this approach facilitates precise analysis, essential for the early detection of cancer. This approach optimizes model performance through fine-tuning, wherein earlier layers maintain learned representations. In contrast, later layers adjust to new task characteristics, enabling effective inference on unseen data across diverse DL applications. In this subsection, a thorough investigation of various studies that explore the application of transfer learning and holography for disease diagnosis is done. [115] significantly contributes by combining DL and Spatial Light Interference Microscopy (SLIM) for label-free colorectal cancer screening. Employing a transfer learning strategy, the authors leverage the pre-trained VGG16 deep network, known for its proficient feature extraction from SLIM images of colon glands. Utilizing VGG16 network parameters in convolutional layers improves performance, overcoming limitations associated with a limited dataset. The classifier demonstrates remarkable results with a 97% accuracy in differentiating cancerous and benign tissue, supported by a substantial ROC curve area of 98% (validation dataset) and

99% (test dataset). Integrating the SLIM whole slide scanner with AI algorithms offers real-time capabilities and introduces innovative software tools for comprehensive image analysis. Their research highlights the time-saving potential of SLIM, improving efficiency for clinicians. The primary challenge in implementing the SLIM whole slide scanner lies in seamlessly integrating workflows, ensuring validation, and addressing financial considerations for successful healthcare adoption.

[116] introduces a successful DL strategy for cell identification and disease diagnosis through DHM, leveraging spatiotemporal information. By incorporating dynamic cellular behavior, this cost-efficient system significantly improves classification accuracy, distinguishing morphologically similar cow and horse red blood cells and diagnosing sickle cell disease in human red blood cells. Their study utilized a recurrent Bi-Directional Long Short-Term Memory (Bi-LSTM) network [117] as the DL model, intricately designed to capture spatiotemporal cellular dynamics within compact digital holographic microscopy constraints. In their work, they used the DenseNet-201 (Densely Connected Convolutional Network-201) [118]CNN, pre-trained on ImageNet, as a feature extractor for classification tasks. [119] introduced TOP-GAN, a novel DL approach for medical imaging that seamlessly combines transfer learning and GANs. The DL model, trained on unclassified images from a different cell type, demonstrates impressive accuracy ranging from 90% to 99% in classifying healthy, primary, and metastatic cancer cells, even with a limited training dataset. TOP-GAN surpasses conventional methods when handling small training sets, showcasing the effectiveness of combining transfer learning and GANs. The authors suggest leveraging MOBILE-NET (Mobile Network) [120] from ImageNet for optimal transfer learning with a small dataset, outperforming alternative methods such as VGG16. Despite the promising results, the study acknowledges limitations attributed to the small training set in DL. The TOP-GAN approach shows potential but is constrained by the scarcity of classified images.

[121] presented a novel live-cell classification approach using a triple-path DL framework, integrating spatial and temporal fluctuation maps with quantitative optical thickness maps. Their study utilized ResNet-50, pre-trained on ImageNet, for cell classification, overcoming gradient challenges through skip connections. The model was trained separately on cell morphology and spatiotemporal maps. Early- and late-fusion techniques optimized discrimination between primary and metastatic cells, refining classification based on distinctive features. Their architecture improves metastatic potential examination over morphological evaluation, highlighting the significance of acquiring cells over time. The study is limited by focusing on two specific cancer cell lines from a single patient, restricting the generalizability to broader cancer types and diverse patient cohorts. [122] employed learning techniques to categorize cells using raw digital holograms. These holograms contain detailed complex amplitude information within modulated fringes. The authors developed a training method using deep and feature-based ML models to extract this information independently of the reconstruction process. Their approach employs Mask R-CNN (Mask Region-based Convolutional Neural Network) [123] for cell segmentation from in-flow DH video frames, and cell masks are reconstructed by fragmenting recorded cells in a petri dish. The training, validation, and test sets are created by combining in-flow Digital Hologram (DH) video frames with fragmented cell masks. Following this, a binary classifier is used to differentiate between different neuroblastoma cell lines using the collected data. Extracted features are analyzed using shallow multilayer perceptron, logistic regression, and a transfer learning-based model, LeNet-like CNN [124]. Combining Mask-R-CNN output with LeNet-like CNN achieved a classification accuracy of 100%, while (Multilayer Perceptron) MLP and logistic regression achieved 92.2% and 95.5% accuracy on the test set.

[125] introduced a novel approach based on Deep Transfer Learning (DTL) to analyze Lens-free Digital In-line Holography (LDIH) images for cellular analysis, particularly in classifying cells based on the number of cell-bound microbeads. The DTL approach achieved higher accuracies compared to other methods, with VGG19-PCA-MLP (VGG19-Principal Component Analysis-Multilayer Perceptron) achieving 75.5% accuracy for holograms and 82.0% accuracy for object images. Their study demonstrates the DTL approach's effectiveness in accurately classifying holograms of cells labeled with molecular-specific microbeads, highlighting its potential to create a cost-effective and portable tool for point-of-care diagnostics, especially in resource-limited settings. [126] proposed a DL method to classify living cells into mitosis and non-mitosis categories using label-free QPI with transport of intensity equation techniques. They utilized a pre-trained DCNN through transfer learning for binary classification of mitosis and non-mitosis. Results show that the network trained with phase images achieves an average accuracy of 98.9% on validation data, outperforming the network trained with intensity images, which achieves an average accuracy of 89.6%. This integration of QPI and DL enables accurate and noninvasive prediction of the mitotic status of living cells.

[127] presented an automated colorectal cancer screening method using DL with SLIM data. A Mask R-CNN algorithm achieved high levels of gland detection and classification accuracy. Using Keras and TensorFlow, the model incorporates a two-CONV-layer branch, leveraging a pre-trained ResNet101 from ImageNet, performing accurate gland detection and classification in SLIM images. This approach exhibits

Table 3. Transfer learning and holography for disease diagnosis.

Reference of paper	Integration Type (Disease type + Imaging technique type + Kind of AI technique)	Dataset	Evaluation Metric
[121], Ben Baruch *et al* 2021	Live colorectal adenocarcinoma cancer cells + Digital off-axis holographic microscope + ResNet-50	Proprietary dataset	Accuracy (89.07 ± 4.23), Sensitivity (88.89 ± 7.50), Specificity (89.32 ± 5.80), Precision (88.26 ± 7.81) and AUC (96.03 ± 2.44)
[127], Zhang *et al* 2022	Colorectal cancer+ SLIM tissue scanner + Mask R-CNN	Private Dataset	Accuracy (91% for gland detection, 99.71% in gland-level classification, and 97% Accuracy in core-level classification)
[115], Zhang *et al* 2020	Colorectal cancer + SLIM+ Transfer learning with VGG-16	Data Available on request	Accuracy (97%), AUC (on the validation set was 0.98, and 0.99 on the test set)
[119], Rubin *et al* 2019	Two pairs of isogenic cell lines: 1) Hs 895.Sk (healthy skin) and Hs 895.T (melanoma), 2) SW 480 (colorectal adenocarcinoma colon cells) and SW 620 (metastatic from lymph node of colorectal adenocarcinoma cells) + Low-coherence off-axis holography + TOP-GAN	In-house Dataset	Sensitivity (98.96%) Specificity (99.61%) and AUC (0.995)
[116], O'Connor *et al* 2020	RBC's from both healthy individuals and those with SCD + Digital Holographic Microscopy + Bi-LSTM network	Dataset not available publicly	Accuracy (81.52%)and AUC (1.00)
[122], Priscoli *et al* 2021	Neuroblastoma cells + Digital holography + Mask-R-CNN(LeNet-like CNN, Multi Level Perceptron and logistic regression)	Available on request	Accuracy(100%,92.2% and 92.5%)
[125], Kim *et al* 2018	Cancer cells (SkBr3, A431) + Lens-free digital in-line holography + VGG19	Collected manually	Accuracy (75.5%), Cohen's kappa (0.687) and Residual Change Index (RCI) value (0.487)
[126], Li *et al* 2021	Living cells mitosis + QPI + Pre-trained DCNN	Collected manually	Accuracy (98.9%)
[128], Lam *et al* 2020	Noncancerous epithelial and fibroblast cell lines, and MDA-MB-231 and MCF-7 Breast cancer cell lines + Digital holographic microscopy + Linear SVMs	Collected manually	Accuracy (96% to 100%)

promising results in colorectal tissue segmentation, classification, and whole-core diagnosis. The SLIM-based tissue scanner eliminates manual segmentation, providing intrinsic tissue markers for clinical use without staining or calibration. It ensures standardization and comparability across instruments and laboratories. In their study, the authors have utilized a tissue microarray containing samples from 132 patients, which may limit its ability to comprehensively represent the diversity and variability of colorectal cancer cases within the broader population. Therefore, validation and testing with more extensive and diverse datasets are required to estimate the generalizability of their proposed approach. [128] proposed a framework for evaluating the morphology of individual cells and detecting any transition in phenotypes within the cancer cell population toward epithelial or mesenchymal cell lines. Their model determines the morphological status of unknown cancer cells by training a linear SVM model on epithelial and mesenchymal cell lines unaffected by cancer. The training data comprises quantitative phase microscopy images of these cell lines. Subsequently, transfer learning is employed to train the same model on MDA MB-231 and MCF-7 breast cancer cell lines with mixed morphology, resulting in an Epithelial-Mesenchymal (EM) score. This score aids in classifying unknown cancer cells situated between the morphological extremes of EM cell lines. Features were extracted from the phase maps reconstructed from each cell line, then transformed using PCA into six PCs, leading to higher accuracy in the linear SVM. The combined use of the linear SVM and 6PCs achieved an accuracy of 95.5% ± 0.3%.

Table 3 comprises studies that utilize the transfer learning approach for analyzing holographic imaging data.

9.4. Holography microscopy and artificial intelligence in eell imaging

This section explores the application of holographic microscopy and AI in cell imaging. [129] introduced the Holographic Reconstruction Network (HRNet), an end-to-end DL framework for digital holographic reconstruction. HRNet tackles critical challenges in holographic reconstruction, including removing unwanted zero-order and twin images, compensation for phase aberrations, and generating all-in-focus

images and depth maps for objects with multiple sections. Remarkably, HRNet acquires noise-free reconstructions without relying on prior knowledge or additional filtering operations, accommodating amplitude and phase imaging while producing accurate depth maps. Further, the framework significantly reduces computation time compared to conventional metric-based methods. It also outperformed traditional approaches in terms of reconstruction quality across various modalities. [130] explore the applications of DL in diverse optical microscopy techniques, improving both image quality and spatial resolution. DL stands out in automating smartphone-based microscopy for remote medical support and is pivotal in enhancing holographic image reconstruction accuracy with minimal hardware needs. However, challenges endure in encoding topology and smoothness for ANNs, necessitating ample annotated data and presenting overfitting risks with smaller datasets. Although DL models demonstrate proficiency on benchmarked datasets, unfamiliar data may introduce challenges and potential imbalances.

[131] present a novel method that combines Digital In-line Holographic Microscopy (DIHM) with AI to measure RBCs' 3D position and orientation. DIHM captures holographic images of RBCs at various out-of-plane angles, overcoming traditional limitations. AI, including DL, augments data and predicts RBCs' out-of-plane angle from holographic images. Numerical reconstruction and ellipse detection then determine the 3D position and in-plane angle. This integrated approach enables measuring individual RBCs' 3D positional and orientational information within a single holographic image. It facilitates analyzing dynamic translational and rotational motions of abnormal RBCs in shear flows, aiding in hematologic disorder research. [132] proposed a holographic imaging scheme utilizing random illuminations and in-line holographic geometry for enhanced reconstruction and twin image removal. The study introduces an unsupervised DL method, specifically an AE model, to address the twin image issue, allowing blind single-shot hologram reconstruction without a pre-existing dataset. This approach efficiently reconstructs amplitude and phase distributions, surpassing CNNs in in-line holography. Experimental results demonstrate the technique's superior ability to reconstruct high-quality quantitative images compared to traditional methods. Study limitations include the 'black box' nature of the auto-encoder model, potential subjectivity in weight adjustments, and reliance on factors like delta correlation. Further research is needed to explore generalizability, computational complexity, hardware requirements, scalability, and practical validation.

[133] introduced a single-shot phase-shifting interference microscopy technique using DNNs for high-resolution QPI in MG63 osteosarcoma cells related to bone cancer. Leveraging 240 datasets and 1200 interferometric images for training and testing, the study demonstrates the method's effectiveness in achieving high-resolution phase imaging for biomedical analysis. Overcoming traditional limitations, it improves sensitivity for live-cell imaging, emphasizing its versatility for industrial and biological samples. The research utilizes DNNs and GANs to generate and compare phase maps with experimentally recorded interferograms in single-shot phase-shifting interference microscopy. The study emphasizes high-resolution quantitative phase mapping, potentially restricting its use in other imaging methods. It explicitly investigates extracting step heights beyond half the wavelength in single laser-based QPI. [134] introduced Partially Spatially Coherent Digital Holographic Microscopy (PSC-DHM), a QPI method integrated with a DNN to explore homogenous RBCs and highly heterogeneous macrophages. Their approach optimizes coherence properties and numerical aperture to improve spatial sensitivity and resolution. GAN is utilized to enhance the generation of high-resolution phase images trained with LR-HR datasets from the partially PSC-DHM system. The suggested PSC-DHM + GAN method holds promise for label-free tissue imaging, disease classification, and high-resolution tomography applications. The study envisions future applications in capturing neuronal movements, high-speed imaging of sperm cells, whole tissue slide imaging, and material sciences, providing enhanced resolution and sensitivity in larger areas.

In their study, [135] addresses the limitations of bright field microscopy in sperm cell selection for IntraCytoplasmic Sperm Injection (ICSI). Their integration ofPSC-DHM with a DNN achieved high sensitivity, specificity, and accuracy in classifying normal and stress-affected sperm cells. The research highlights the impact of cryopreservation, hydrogen peroxide exposure, and ethanol on sperm subcellular structures detected through the PSC-DHM and DNN framework. The proposed QPI + DNN approach shows promise for improving ICSI and assessing semen quality, addressing the global decline in male fertility. ResNet-101 achieves an average accuracy of 85.6%, outperforming other architectures, with the DNN effectively distinguishing between normal and stress-affected sperm cells. Challenges in sperm cell classification using QPI involve issues like the absence of chemical specificity, inadequate morphological details, and difficulty in detecting subtle subcellular changes. The variation in the training approach and the constrained sample size of 10,163 sperm cells might affect the overall generalizability and precision of the study.

[136] introduced a non-invasive method for phase imaging biological cells through white light interferogram and Hilbert transform color fringe examination. This technique enables refractive index determination and extraction of morphological features, providing a cost-effective and user-friendly solution. Experimental results showcase the successful

phase imaging of human RBCs and onion cells. While the approach exhibits potential for diverse applications in QPI, one limitation is the requirement to integrate AI, ML, or DL techniques for improved visualization and analysis of biological cells. [137] present a single-shot white light interference microscopy approach for QPI of biological cells, focusing on the wavelength-dependent imaging of human RBCs. The developed method allows fast and accurate analysis of dynamic biological samples with millisecond-level path-length changes. Using a common path white light interference microscope and a three-chip color CCD (Charge-Coupled Device) camera, colorful interferograms are recorded and decomposed for analysis. The Local Model Fitting (LMF) algorithm ensures prompt and precise reconstruction of the phase map. The study indicates the necessity to incorporate DL strategies in analyzing biological data obtained through holographic imaging, urging additional exploration in this domain.

[138]'s primary contributions include the introduction of 'HoloForkNet,' a deep-multibranch neural network model designed for reconstructing 3D scenes from single inline holograms. This innovative model effectively tackles the challenges of reconstructing off-axis and inline holograms, managing phase-only objects, and eliminating noise from the reconstructed images. It demonstrates outstanding performance by achieving high-quality image reconstruction for scenes comprising up to eight planes, with an average Structural Similarity Index Metric (SSIM) of 0.94 for 3D test scenes. The architectural design, inspired by U-Net and featuring decoder-encoder architecture with skip connections, facilitates the reconstruction of 3D scenes composed of distinct 2D object planes, each having its independent decoder pathway.

[139] introduced a novel multi-modal system merging fluorescence microscopy and QPI, offering simultaneous molecular specificity and phase information acquisition. Using a single-chip color CCD camera, the system monitors dynamic morphological changes in MG63 osteosarcoma cells, providing quantitative data on cellular adhesion for potential disease detection. The study addresses challenges in QPI by reducing speckles and spurious fringes through a specially designed pseudo-thermal laser light source. It employs fourier fringe analysis to reconstruct phase maps, delivering valuable insights into biophysical parameters like refractive index and cell morphology. However, the study needs DL algorithm integration, leading to a gap in performance analysis accuracy. Additionally, it does not address spatially coherent light source challenges, lacks comparisons with existing techniques, and omits generalizability and imaging speed information.

Table 4 showcases various studies that merge holography microscopy with AI for diverse cell imaging applications. After analyzing various relevant studies concerning this integrative approach, we identified different challenges associated with this integration, as depicted in the subsequent section. Further, the literature on cancer diagnosis demonstrates limited exploration of integrating holographic imaging and DL for analyzing various types of carcinomas. Thus, further research is essential to develop an innovative approach that combines holographic imaging's three-dimensional visualization with DL's analytics, addressing existing gaps in cancer diagnosis. Critical limitations in existing studies include limited dataset availability and the non-collaborative nature of universities and institutes, highlighting the importance of collaboration among institutes to overcome these challenges. Other identified deficiencies include the need for advanced techniques like ViTs and XAI in current literature. Therefore, future efforts must aim to leverage advanced DL strategies, such as attention-based models like U-Net attention, ViTs, and XAI techniques like GRAD-CAM. These methods aim to improve diagnostic accuracy and provide a comprehensive solution for cancer diagnosis.

10. Challenges in integrating holography imaging and deep learning for cancer Diagnosis

Integrating holography microscopic imaging and DL for cancer diagnosis holds tremendous potential for revolutionizing cancer diagnostics. However, this innovative approach faces several challenges that need careful consideration discussed as follows:-

- **Limited availability of holographic medical imaging datasets** Firstly, the shortage of holographic medical imaging datasets accessible to the public represents a notable obstacle. Obtaining meticulous and diverse datasets is crucial for training and validating DL models, yet the limited availability hinders progress in this field.
- **Processing complexity of volumetric holographic data** Secondly, the three-dimensional nature of holographic imaging datasets presents processing complexity. Examining volumetric data requires robust computational resources and efficient algorithms capable of handling their intricacies.
- **The challenge of interpreting DL models in medical practice** Thirdly, a challenge lies in medical professionals' interpretation of DL models. The intrinsic complexity of DL often characterizes models as 'black boxes,' creating difficulty for doctors to comprehend the rationale behind specific decisions made by the model.
- **Development challenges in real-time diagnostics** Transforming the amalgamated methodology into real-time biomarkers for practical clinical applications poses another substantial barrier. Translating this integrated approach into a functioning real-time diagnostic tool necessitates advanced facilities,

Table 4. Holographic imaging and artificial intelligence in cell structure visualization.

Paper Reference	Algorithm Used or Developed	Study Type
[129], Ren *et al* 2019	Holographic Reconstruction Network (HRNet)	The HRNet framework is specifically crafted to study diverse sample types and efficiently reconstruct their holographic images.
[130], Melanthota *et al* 2022	Various DL algorithms have been reviewed	The samples studied include biomedical samples, tissue samples, blood smear samples, and DNA samples.
[131], Kim *et al* 2023	CNN	This study introduces an innovative image-based approach for determining normal RBCs' 3D position and orientation utilizing DIHM combined with AI.
[132], Manisha *et al* 2023	Autoencoder	Their study demonstrates a holographic imaging scheme using random illuminations, numerical reconstruction, and twin-image removal.
[133], Bhatt *et al* 2021	MS-QPI + DNN + GAN	The samples studied in this paper are: Optical waveguide and MG63 osteosarcoma cells
[135], Butola *et al* 2020	DNN	The study examines human sperm cells under different stress conditions like cryopreservation, hydrogen peroxide exposure, and ethanol exposure to assess their morphology and quality.
[140], Bhatt *et al* 2022	QPI+DNN	The samples studied in this paper are:Optical waveguide and MG63 osteosarcoma cell
[134], Butola *et al* 2020	GAN	The study utilizes human RBCs and macrophages to evaluate a new DHM system with DNN.
[136], Srivastava and Mehta, 2013	Hilbert transform color fringe analysis technique	The Hilbert transform color fringe analysis technique is used to quantitatively obtain the phase map of onion and human RBCs from white light interferograms.
[137], Mehta *et al* 2016	Local Model Fitting (LMF) algorithm	The study focuses on QPI of RBCs using single-shot white light interference microscopy and the LMF algorithm.
[138], Svistunov *et al* 2023	Hologram Forked Network (HoloForkNet)	The study focused on reconstructing 3D scenes from digital holograms using HoloForkNet and tested it on holograms with varying resolutions.
[139], Tayal *et al* 2020	2D Phase Unwrapping Algorithm and Fourier Fringe Analysis Method	The study investigates morphological changes and cellular adhesion/spreading in MG63 osteosarcoma cells using fluorescence microscopy and QPI.

academically rich collaboration, robust infrastructure, and meticulous attention to various technical and operational hurdles.

- **Generalization challenges across diverse cancer types** Another, challenge lies in the necessity for a unified approach capable of effectively generalizing across diverse cancer types. The unique holographic characteristics inherent to various cancer types may require the development of specialized DL models.
- **Challenges in clinical validation and collaboration** Moreover, clinical validation and collaboration present significant hindrances, necessitating strict testing protocols, diverse datasets, and adherence to healthcare standards. Locking the gap between research and practical implementation is essential for boosting credibility and effectiveness in cancer diagnosis.
- **Ethical concerns and patient data privacy** Finally, Ethical concerns and patient data privacy become another essential challenge when collecting datasets from collaborating hospitals. Ensuring patient information's confidentiality and honest use is crucial for maintaining trust and adhering to ethical standards.

In the subsequent section of this paper, we delve deeply into the discussion, meticulously exploring the findings and their implications.

11. Discussion

Traditional medical imaging modalities lack in-depth and detailed anatomical analysis, hindering accurate cancer diagnosis. This study aims to investigate the collaborative potential of DL and holography microscopic phase imaging for enhancing cancer diagnosis. The work elucidates the holography microscopy imaging method, detailing its process of capturing and reconstructing three-dimensional representations of microscopic biological tissues under examination. Holography microscopy utilizes light interference patterns to create intricate, three-dimensional images of cancerous tissues, demonstrating their detailed structure. This technique offers detailed visualization of cell morphology and the tumor microenvironment with high resolution and depth. Holography microscopic imaging, capable of capturing both phase and amplitude details, enhances visualization, especially in-depth perception. Therefore, researchers gain crucial insights into cancer biology, improving diagnosis and treatment strategies.

The advanced analytical ability of DL in determining complex disease patterns is profound. Utilizing state-of-the-art algorithms and comprehensive datasets, DL models illustrate exceptional proficiency in identifying subtle features and patterns within medical

data or images, which could otherwise be overlooked by human observers, specifically in cancer diagnosis. This proficiency guarantees precise identification and classification of diseases at their early stages, encouraging timely interventions. In this research study an extensive literature review covering ML, DL and holographic cell imaging has been conducted. As per this research study, several research efforts globally have successfully integrated holography and DL methods for cell imaging. However, there has been limited research focused on diagnosing cancers using AI applied to holographic imaging modalities. One reason for this could be the limited availability of publicly accessible datasets, along with the restricted collaboration between institutions on data sharing, which exacerbates this gap and hinders progress in the field. Therefore, it is crucial to address this gap to further enhance comprehension and innovation in diagnosing specific carcinoma types. By bridging this divide, valuable insights can be shared within the scientific community, thereby fostering collaborative efforts to address the intricate complexities of various cancers by integrating advanced imaging techniques and DL algorithms.

The study highlights the significant benefits of this integration for cancer diagnosis. DL algorithms, particularly CNNs, famous for feature extraction, when combined with rich, informative holographic cell imaging data, significantly enhance medical data analysis. This integration not only facilitates early cancer detection but also supports automated, detailed anatomical analysis, accelerates diagnoses, and enables personalized treatments. These advances in DL algorithms will help in improving healthcare outcomes thereby, enabling early detection and supporting scientific social responsibility through better medical data analysis. A comprehensive methodology is explained in detail, which can guide future interested researchers in addressing challenges within this field. Advanced DL approaches, such as attention mechanisms (e.g., ViTs), XAI techniques (including Grad-CAM, Grad-CAM++, and SHAP), and LSTMs, when integrated with holographic data, can greatly improve the extraction of meaningful insights from medical datasets. These advancements contribute to a deeper understanding of diseases and the development of improved treatment approaches. Various strategies, including synthetic data generation and transfer learning, are explored in depth to address the challenges posed by small and imbalanced medical datasets. Other challenges associated with this novel integrative approach include ethical concerns related to patient data privacy and difficulties in generalizing across various cancer types, as well as ensuring clinical validation and fostering collaboration. Therefore, addressing these challenges is crucial to fully unlocking the potential of this integrated approach for cancer diagnosis. The most intriguing aspect of this study lies in its emphasis on future research, highlighting a notable gap in integrating holographic imaging with DL for cancer diagnosis. Recommendations include fostering collaboration among institutes to address the scarcity of holography imaging datasets, which could lead to advancements in cancer diagnosis and treatment strategies. After thoroughly examining the findings and implications of this integrated approach, the subsequent section of this paper outlines future research directions.

12. Future work

A thorough literature review has uncovered a significant research gap in integrating holography microscopic imaging with DL for precise carcinoma diagnosis. While studies have successfully merged holography and DL globally, particularly in diagnosing lung, colorectal, breast, and ovarian cancers, there remains limited exploration into other cancer types. This lack of investigation is primarily attributed to the absence of publicly available datasets and insufficient collaboration among institutes, delaying progress in this area. Addressing this gap is crucial for advancing knowledge and innovation in diagnosing various carcinoma types. It allows valuable insights to be disseminated within the scientific community and fosters collaborative efforts in addressing cancer complexities by integrating advanced imaging techniques and DL algorithms. Furthermore, efficient algorithms are required to manage the processing complexity of three-dimensional holographic imaging datasets, including exploring methods for efficiently examining volumetric data. A key future research direction focuses on ensuring clinical validation and fostering collaboration to bridge the gap between research and practical application in cancer diagnosis. This includes establishing rigorous testing protocols and leveraging diverse datasets that comply with healthcare standards to improve credibility and effectiveness. Researchers can explore methods to address ethical concerns and patient data privacy by implementing federated learning to integrate holography microscopic imaging with DL in carcinoma diagnosis. Federated learning enables collaborative model training across healthcare institutions without sharing raw data, ensuring privacy, enhancing dataset diversity, and fostering ethical collaboration, thereby accelerating cancer diagnosis progress. Additionally, there has been no work to date that applies holographic imaging data for cancer diagnosis using reinforcement learning. Another promising future research direction involves leveraging XAI techniques to address the black-box nature of DL models applied to holographic data, which remains a largely underexplored area. Therefore, researchers can explore this novel approach to potentially enhance diagnostic accuracy and model performance by leveraging reinforcement learning techniques. After

presenting future research directions, this study is concluded in the following section.

13. Conclusion

The collaboration between DL and holography microscopic imaging holds significant promise in cancer diagnosis, supplementing traditional imaging modalities such as MRI, CT, ultrasound, and PET by offering comprehensive anatomical insights. This review study thoroughly examines existing literature, highlighting key advancements, identifying research gaps, and outlining potential avenues for future exploration. It emphasizes the critical need for further investigation into the integration of QPI and DL to improve diagnostic accuracy. The research introduces a novel approach by combining QPI and DL, offering a promising enhancement to cancer diagnostic capabilities. The analysis demonstrated a scarcity of studies integrating QPI and DL for cancer diagnosis, with a predominant focus on specific cancer types rather than a broader range. Furthermore, most research primarily focuses on holography cell imaging, often neglecting the integration of DL strategies. Consequently, this research gap is identified as a critical objective for future investigation. The proposed methodology comprises several essential steps. Initially, targeted tissue samples will be gathered from the collaborating institute or hospital. These samples will be scanned using a DHM at the designated facility. After obtaining annotated imaging datasets, any required preprocessing techniques will be applied to address potential imbalances in the data. Subsequently, DL models will be trained using architectures like CNN, U-Net, and ViTs. Furthermore, the incorporation of XAI techniques within DL frameworks is recommended to provide a deeper understanding of the decision-making processes involved in medical imaging analysis, thereby enabling more comprehensive disease diagnosis and identification. This study highlights the benefits of integrating holographic imaging and DL for precise cancer diagnosis. Additionally, it provides an in-depth discussion of the challenges associated with this integration methodology, revealing the complexities and obstacles that must be addressed for optimal cancer diagnostics.

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Ethics approval and consent to participate

In compliance with ethical standards, this research, which does not involve human participants, adheres to established guidelines and principles, emphasizing the integrity and responsible conduct of the study.

Research involving human participants and/or animals informed consent

This research does not involve the participation of human subjects and/or animals.

Informed consent

This research does not involve the participation of human subjects and/or animals. Therefore, no such consent was required.

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Disclosure of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

No data has been analyzed in this paper; the studies presented were reviewed, and based on those, essential research gaps and future research directions were identified.

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