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Current trends of artificial intelligence and applications in digital pathology: A comprehensive review

Neelankit Gautam Goswami [1], Shreyas Karnad [1], Niranjana Sampathila [1,*], G. Muralidhar Bairy [1], Krishnaraj Chadaga [2], K. S. Swathi [3]

[1]*Department of Biomedical Engineering, Manipal Institute of Technology (MIT), Manipal Academy of Higher Education, Manipal, India*
[2]*Department of Computer Science and Engineering, Manipal Institute of Technology (MIT), Manipal Academy of Higher Education, Manipal, India*
[3]*Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, India*

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ABSTRACT

Digital pathology is a field that blends various techniques for obtaining, analyzing, sharing, and saving information about pathology. This information often comes from digitized microscope slides. Digital pathology also uses artificial intelligence (AI) to help reduce errors made by humans. This review talks about digital pathology and the new techniques linked to it. Instead of traditional microscopes, digital pathology employs virtual microscopy and whole-slide imaging. It marks a major improvement over old pathology methods, which had several problems. Digital methods use computers and machines to solve these issues. The basic process of digital pathology has three parts: the input stage, the analysis stage, and the output stage, which includes storing the information. This review focuses on two main techniques: object detection and its smaller methods, and the use of AI and its specific approaches like explainable AI (XAI) and deep learning. The paper also discusses various deep learning methods, mainly used to detect different types of cancer. It also acknowledges that not every method is perfect, so we discuss various challenges and limitations of digital pathology techniques that need to be solved before these methods can be widely used.

1. Introduction

Pathology refers to studying how a disease or an injury affects the body. When we consider the broader scope, pathology means the study of conditions. Still, when it comes to medical treatment, this scope gets shortened to something that is called general pathology. General pathology deals with a variety of procedures for disease diagnosis by analyzing body fluids samples (Block and Algeciras-Schimnich, 2013), tissue samples, and cell samples. Pathology can also mean a disease's prediction or actual spread (progression), such as cancer. Technically, this is referred to as pathophysiology (Park, 2008).

Conventional pathology methods like microscopy and slide analysis without computer imaging have many drawbacks for doctors, like time (Trotter et al., 2009), contamination (Hunt, 2008), human errors, etc. After submitting the affected or sometimes even non-affected patient sample, it takes a lot of time to manually analyze the sample and give the result (Trotter et al., 2009). More time can result in the sample losing the desired part to be analyzed. Also, the samples must be sent to equipped laboratories if the analysis cannot be performed locally. However, during the transit phase, the sample can be contaminated by various factors, such as mishandling, surrounding climate, and mixing of the samples (Hunt, 2008). And lastly, as there is no computer involvement or automated techniques to analyze the sample, it is analyzed manually. However, there can be an error in the analysis if the person is not well-trained (Hollensead et al., 2004). There can be false positives or, even worse, false negatives for deadly diseases such as cancer or SARS-Cov2 (Mouliou and Gourgoulianis, 2021).

In contrast, digital pathology, a branch of pathology, utilizes information management from

* Corresponding Author.
Email Address: niranjana.s@manipal.edu (N. Sampathila)
https://doi.org/10.21833/ijaas.2023.12.004
Corresponding author's ORCID profile:
https://orcid.org/0000-0002-3345-360X

digital slides. This approach replaces traditional microscopy with digital microscopy. Here, glass slides are converted into digital slides, allowing them to be displayed, examined, and shared on a computer screen. This process, known as Whole Slide Imaging (WSI) or virtual microscopy, enables digital pathology to be applied in various areas. The aim is to enable more affordable diagnosis and disease prediction by leveraging developments in artificial intelligence (AI) and machine learning (ML). Fig. 1 presents a brief walkthrough of this review paper. It shows all the sections that we have discussed here in correspondence to digital pathology.

Fig. 1 shows the systematic structure and flow that will be covered in this particular review paper.

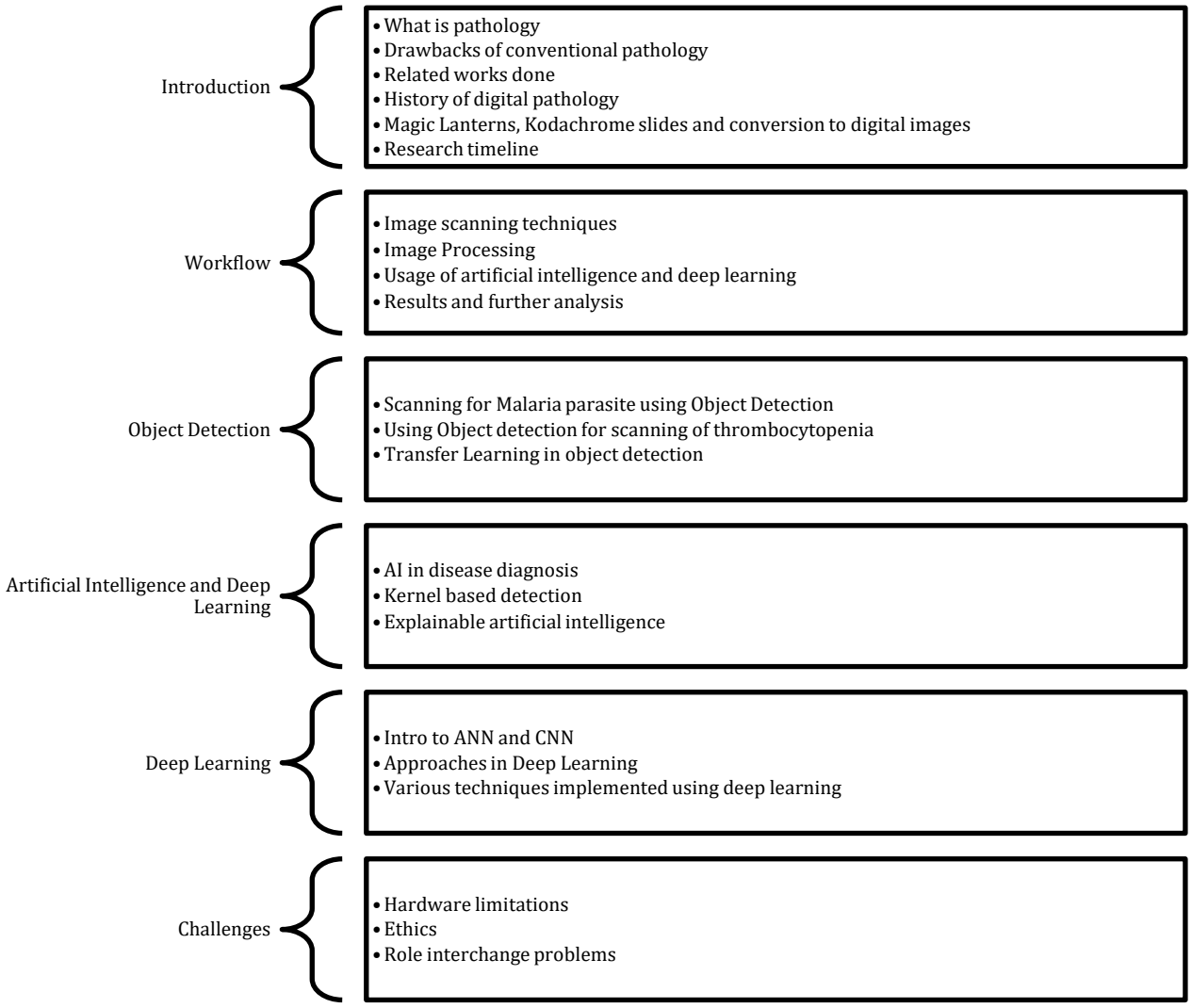

Fig. 1: Structure and flow of review

Despite being a relatively new area, the origins of this field trace back over a century, with telepathology emerging in the 1960s. From the 17th century to the 1850s, Magic Lanterns were used to project microscope images. These slides were made using albumen (Morrison and Gardner, 2015). Subsequently, a technique known as Kodachrome slides, developed by Kodak, came into use. These slides remained prevalent for pathology purposes until the 1980s (Morrison and Gardner, 2015). Currently, with specialized equipment, these slides can be readily transformed into digital format.

With the invention of the microscope over 250 years ago, its use for pathology was also boosted (Majno and Joris, 1973; Wright, 2018). The technique of WSI goes back to the late 1990s (Pantanowitz et al., 2011). Fig. 2 represents the year-wise total papers published about digital pathology since the 20th century. Fig. 2 also shows the critical milestones in the field, which can also boost the research in specific scenarios.

As mentioned previously, the research has been going on since the 20th century. In the following graphs, we have given the number of articles that were published on the topic of digital pathology techniques in the fields of oncology and histopathology. Both of these graphs are derived from Fig. 2 itself, but they are subdivided into two sections to help the readers understand how much research was conducted in the sub-fields of digital pathology. Fig. 3 shows the number of digital pathology papers that have been published on Oncology with the PubMed search engine.

Similarly, Fig. 4 shows the digital Pathology papers on histopathology on PubMed.

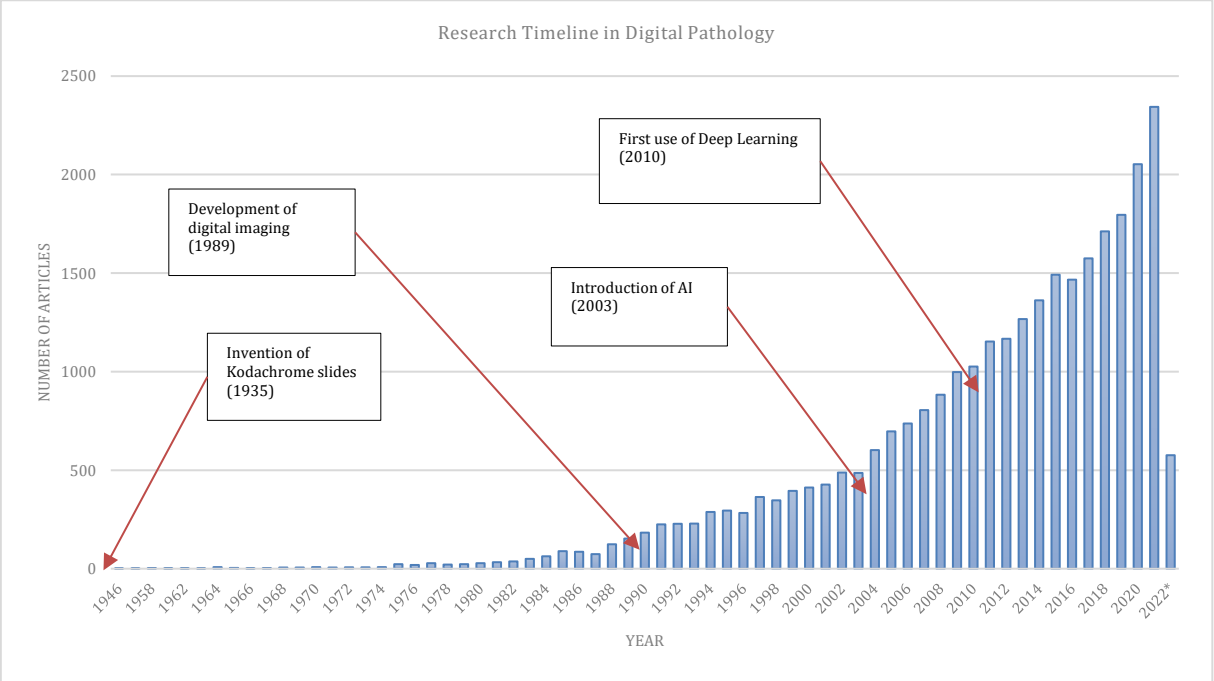

Fig. 2: The timeline of research conducted in digital pathology

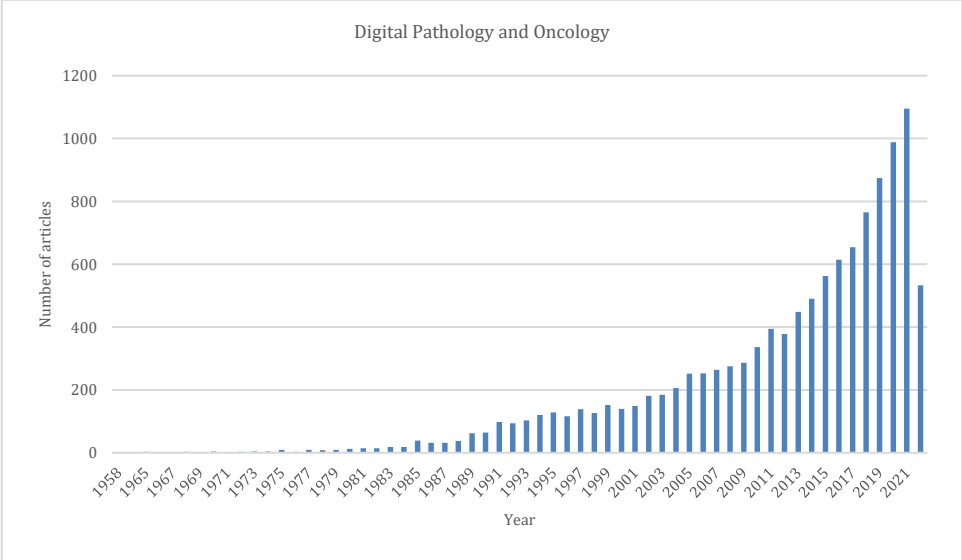

Fig. 3: Digital pathology papers on oncology on PubMed

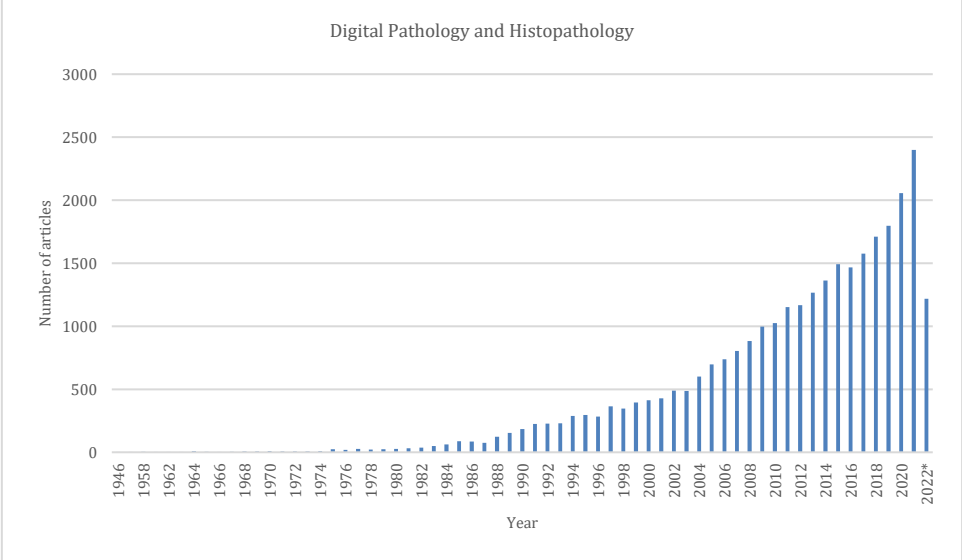

Fig. 4: Digital pathology articles on histopathology on PubMed

While the 20th century saw a significant rise in research, it rocketed to a great extent in the 21st century. Per year, we saw an average of 1.5k papers getting published. The novelty of our review article is as follows:

- An in-depth review of object detection in digital pathology has been conducted.
- A comprehensive review of various AI applications for digital pathology has been conducted. It includes disease diagnosis, kernel-based detection, and explainable AI (XAI).
- Deep learning applications for digital pathology have been reviewed.
- Various challenges in digital pathology have been discussed.

2. Basic workflow of digital pathology

In the context of Digital Pathology, there are various algorithms, most of which encompass four fundamental steps, and occasionally, additional steps are involved (Aeffner et al., 2019). Fig. 5 illustrates the general concept of the workflow for an intelligent algorithm. It is important to note that Fig. 5 represents a generic workflow and is not specific to any particular algorithm. Although algorithms may share a similar workflow structure, their core functionalities can differ.

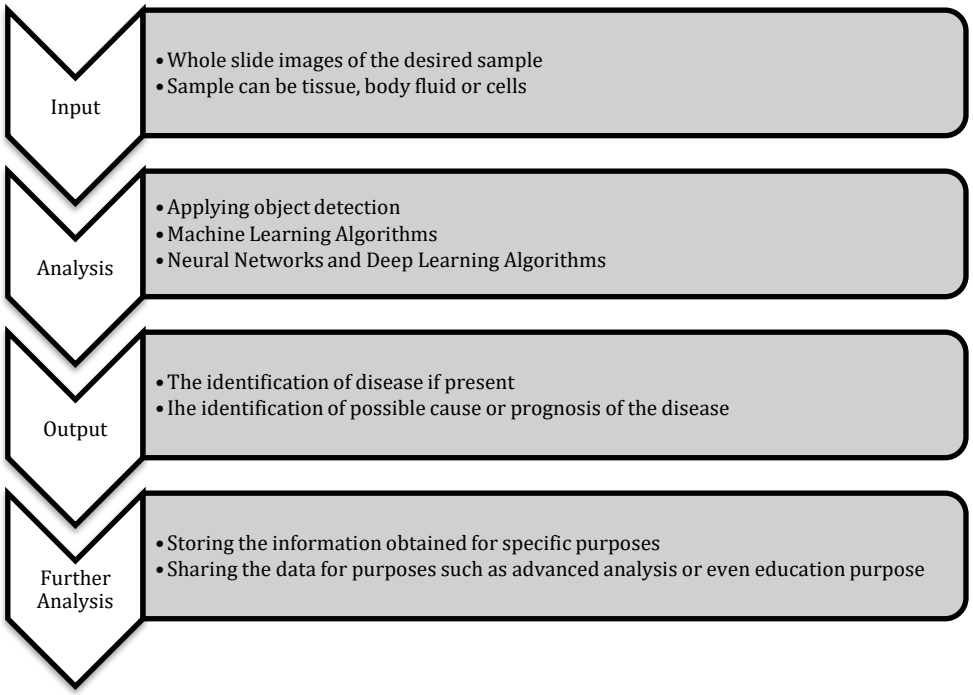

Fig. 5: Workflow of digital pathology by incorporating intelligent algorithms

The glass slides are upgraded with a specialized scanner, so digitalized slides (Hou et al., 2016). It must be made sure that these scanned slides are free of debris like grime, scratches, and other blocking factors. Two procedures are used for scanning: line-based scanning and tile-based scanning. This is done with the help of motorized stages and cameras. In the case of tile scanning, the scanner captures square field-of-view pictures of the entire tissue, while in the case of line-based scanners, the tissue pictures are long, non-interrupted lines(stripes). Later, these tiles or lines are joined to form one single image. We can also use these machines for deep learning algorithm training later. The images created by scanning are analyzed on computer systems by object detection algorithms or AI-based algorithms such as CNNs (Khosravi et al., 2018) or even deep learning algorithms (BenTaieb and Hamarneh, 2019). The results obtained from the algorithms give information about the disease, if any, and the prognosis of the disease, such as the progression of cancer (He et al., 2021). Data management comes into the picture when the tissues and slides data is stored for further use or can even be supplied to educational institutes for academic purposes.

3. Object detection in digital pathology

Object detection is a computer vision technique to identify and locate objects within an image or a video. To be precise, object detection creates bounding boxes around these identified objects, allowing users to find where desired objects are in (or in what way they are moving) a given picture or scene. Object detection is often mistaken for image recognition. Image recognition labels an image. In comparison, object detection draws a box around each object of interest in an image and labels it. Object detection techniques make use of ML-based models and deep learning-based models. If we talk about object detection in digital pathology techniques, then we need it to detect, let's say, the affected part of the tissue. For example, two software applications called Icy and Cytomine are open source

for detecting and analyzing glomeruli in the images, as demonstrated by Marée et al. (2016). Afterward, supervised classification and even feature extraction can be done using classifiers like WND-CHARM (Orlov et al., 2008)

Shet et al. (2015) developed a method based on image processing for scanning malaria. This method involves a five-step process beginning with capturing images of blood smears under a microscope. The images are then converted to a binary format, and extraneous objects are removed. Following this, red blood cells (RBCs) are isolated by overlaying the binary image onto the original one. For extracting the parasite from the RBCs, the Q component in the YIQ color space is identified. This is achieved by setting a threshold value to segment the parasite region. Next, the "on" pixels in the binary area are counted to determine the parasitic region's size. Another threshold value is then used to classify the image as either non-malarial or malarial. Fig. 6 displays blood smear images at various levels of microscope magnification for malaria parasite scanning. A closer examination of Fig. 6d reveals the presence of a purple-colored parasite in one of the cells.

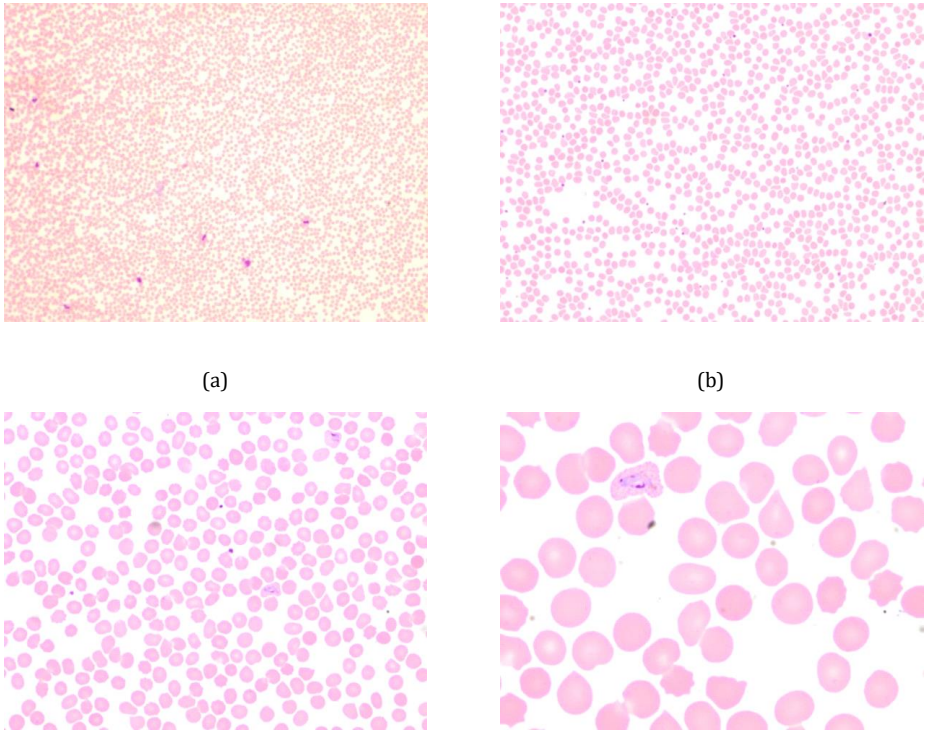

Fig. 6: Acquired blood images with different levels of magnification (a) 100X, (b) 200X, (c) 400X, and (d) 1000X

Mayrose et al. (2021) created an object detection algorithm to identify thrombocytopenia from blood smear images. Thrombocytopenia is a condition where the blood platelet count drops below 150,000 per microliter of blood, resulting in a slower clotting rate and, in severe cases, potentially fatal excessive bleeding. Determining the cell count is crucial to assess if the platelet number is adequate. However, manual counting is prone to inaccuracies and human errors. The object detection algorithm offers a solution by automating cell counting and specifically identifying platelets among all blood cells. Fig. 7 illustrates the workflow of this algorithm.

In the preprocessing stage, the Red (R), Green (G), and Blue (B) channels of the image were separated. It was observed that the Green (G) channel particularly enhances the image at 100x magnification, improving the contrast. Following this, blob detection was applied to the processed images. Blobs are defined as connected regions in an image that share certain properties. The chosen parameters were designed to ensure that only a platelet is identified as a blob, which is then marked as a key point, as depicted in Fig. 8. Fig. 8 presents the outcome of the blob detection on the images, where the dark patches represent the platelet cells. These blobs are subsequently counted to determine if a patient has thrombocytopenia.

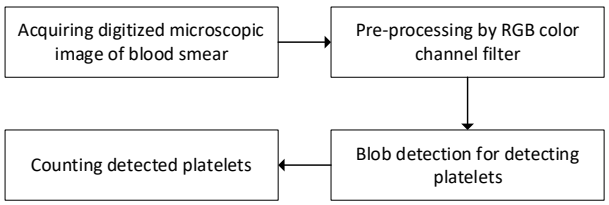

Fig. 7: Workflow of thrombocytopenia detection algorithm using computer vision (Mayrose et al., 2021)

The counted blobs indicate the number of platelets in each image. A threshold of 150,000 platelets per microliter is then applied, as this is the benchmark for thrombocytopenia. If the number of

detected blobs falls below this threshold, the test indicates a positive result for thrombocytopenia. The algorithm developed for this purpose demonstrated an accuracy of 96.4% in detecting thrombocytopenia. Additionally, object detection has been employed in the analysis of various diseases beyond histopathology, including oncology. Table 1 presents a summary of object detection experiments conducted for the detection of cancer and other diseases, showcasing the versatility and application of this technology in different medical fields.

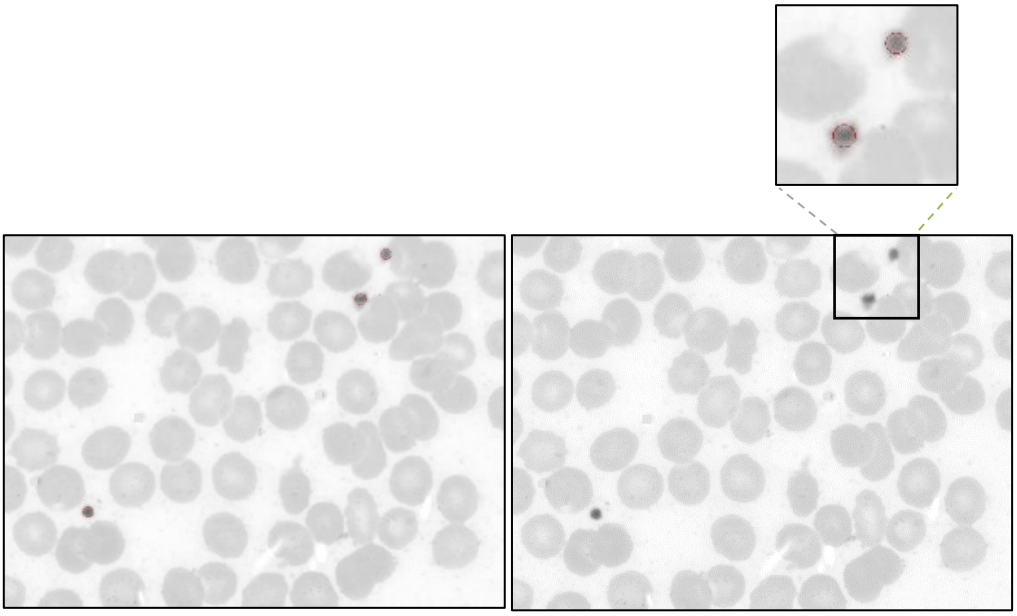

Fig. 8: The blood smear image after applying blob detection (Mayrose, et al., 2021)

Table 1: Object detection experiments conducted for cancer and other diseases detection

Description	Reference
The methodology they developed focuses on identifying sickle cells in blood images using object detection. The preprocessing stage involves converting the images to grayscale and eliminating noise with a median filter. The image is then distinctly partitioned using a technique known as watershed segmentation, as described by Levner and Zhang (2007). Following this segmentation, the number of sickle cells is determined by calculating the properties of each region.	(Kiruthika et al., 2022)
They introduced an end-to-end method for detecting breast cancer through the analysis of mitotic nuclei identification. This process involves using a deep object detection-based approach, specifically an R-CNN mask, to select candidate regions. In the second phase, the precision of these selected regions is enhanced by refining them using a multi-object loss function. The identification of cancer cells is facilitated by this method, as mitotic nuclei serve as a prognostic biomarker for breast cancer.	(Sohail et al., 2020)
A two-layer approach was implemented for the detection of infected cells. In the first layer, a Faster-RCNN model is used to isolate and crop images of cells that are suspected to be infected. The second layer then processes the output from the first layer, classifying whether the cells are indeed infected or not. This algorithm was subsequently tested on a publicly available database to evaluate its effectiveness.	(Manku et al., 2020)
An approach was proposed to characterize Iron Deficiency Anemia (IDA), which is marked by three types of Poikilocyte cells: Dacrocytes, Elliptocytes, and Schistocytes. This approach incorporates the use of ML algorithms such as neural networks, Support Vector Machines (SVM), and K-nearest neighbors (KNN). The appropriate classification of these cell types is determined using the Maximum Voting theory, which involves aggregating the predictions from different algorithms to make a final decision.	(Lotfi et al., 2015)

4. AI in digital pathology

In the past decade, significant progress has been made in integrating AI into the field of pathology. However, it will still require some time before AI can be routinely utilized in daily pathology applications. The creation and storage of digitalized slides have now become more cost-effective. Despite this, AI applications in pathology are still in the early stages of development, often referred to as the beta or basic research phase, and exhibit a wide range of diversity. The last ten years have seen the growth of ML in the area of WSI. Therefore, following the advancements in immuno-histochemistry and next-generation sequencing, AI is often regarded as the third major revolution in this field (Madabhushi and Lee, 2016; Niazi et al., 2019; Salto-Tellez et al., 2019). Even a minor mistake in medical diagnosis can result in over- or under-treatment, which can be particularly critical in serious conditions. For instance, administering chemotherapy to someone without cancer can be fatal. Therefore, it is essential to establish and test the reliability and certainty of medical diagnoses. Medical AI has enormous potential to provide support in this area, but its use is also dependent on resolving various legal and ethical issues. Despite these challenges, AI has distinct advantages in applications with specific, defined goals. In the coming years, AI is expected to become increasingly useful for pathologists. It can address a range of problems in Digital Pathology (DP), offering more efficient, accurate, and cost-effective solutions compared to traditional methods. The use of AI can significantly enhance the precision of diagnoses, thereby reducing the likelihood of errors that could lead to improper treatment. With its ability to analyze large datasets and recognize patterns more efficiently than humans, AI has the potential to revolutionize various aspects of pathology.

Lymph node metastasis recognition is a critical component in cancer therapy. In some cases, lymph

nodes affected by cancer are large enough to be visible either directly or through radiological imaging. However, there are instances where more detailed analysis is required, as is the case with sentinel lymph node evaluation. This evaluation process involves step sectioning of the lymph node at intervals of 200μm or less, resulting in 15 to 20 separate levels on slides for a single lymph node. Such detailed evaluation is particularly important for certain types of cancer, such as malignant melanoma or breast cancer, as highlighted by Nakamura (2019). The process, however, is labor-intensive and prone to errors. Challenges arise due to the rarity of recognizable events, the high level of repetition in the images, and the typically small size of tumor deposits. These factors can make it difficult to accurately identify and assess metastasis in lymph nodes, which is crucial for determining the appropriate course of treatment for cancer patients. The precision and thoroughness required in this evaluation highlight the need for meticulous attention to detail, as any oversight can impact the subsequent treatment decisions and patient outcomes.

For immunohistochemistry, one application is on-slide quality control verification. For immuno-histochemistry accuracy verification, on the slide where a patient's tissue sample is present, additional cultured cell lines or tissue pieces are positioned and stained. They are scanned under a microscope for staining intensity and true positive or negative staining. As observed in histopathology, such evaluation is done with a lot of runs and days by image similarity evaluation (Hegde et al., 2019).

Khandekar et al. (2021) developed a method for diagnosing Acute Lymphoblastic Leukemia by identifying leukemic cells in blood smears using AI, as outlined by Farahani et al. (2015). This method employs the YOLOv4 algorithm, described by Bochkovskiy et al. (2020), which involves a four-step analysis. The process starts with input data comprising blood smear images that contain both healthy and leukemic (blast) cells. These images undergo preprocessing to be compatible with the YOLO algorithm, which is similar to Fully Convolutional Neural Networks (FCNNs), as explained by Khosravi et al. (2018). The model's training is conducted using Google Colaboratory, a platform mentioned by Bisong (2019), and its performance is evaluated using the mean Average Precision (mAP) metric, a concept introduced by Beitzel et al. (2009).

4.1. AI in disease diagnosis

In traditional disease diagnosis, the process typically begins with a clinician inquiring about the patient's medical history, followed by a physical examination, based on which the doctor makes a diagnosis (Barabási et al., 2010). However, there's a risk of errors in diagnosis or interpretation by the clinician, which could lead to inappropriate treatment, potentially causing harm or even being fatal (Armstrong and Hilton, 2014). AI offers a solution to mitigate these risks. AI tools are now being used to diagnose various diseases, such as gastric cancer and hepatitis B (Cao et al., 2021). Additionally, AI can assist in predicting genetic mutations. Techniques like Deep Neural Networks (Khosravi et al., 2018), Support Vector Machines (SVMs), and Decision Trees are among the methods utilized for diagnostic purposes.

4.2. Kernel-based detection

To comprehend kernel detection, it's important first to understand what a SVM is. SVMs are a type of supervised ML algorithm equipped with learning algorithms specifically for classification tasks (Suthaharan, 2016). They are often used in image classification. Kernel-based algorithms, of which SVM is a notable example, are utilized for pattern recognition. This recognition is key to analyzing various types of relationships in datasets, including clusters, classifications, and correlations. Pattanaik et al. (2017) developed a method to detect malarial parasites in thin blood smear images. This process is conducted in three stages:

1. Data Pre-processing: This initial stage involves refining the gathered data by removing noise, inconsistencies, and incomplete data. Here, Kalman filtering is used for this purpose (Kuc, 1979).
2. Candidate Selection and Segmentation: In this stage, the background is eliminated to focus on analyzing objects in the foreground. Kernel filtering is applied here, using two color variations to filter out the required data (Yilmaz et al., 2006).
3. Feature Extraction: The final stage again employs kernel filtering. This step is crucial for extracting specific features from the data, which aids in the accurate detection and analysis of the malarial parasite.

Overall, this three-stage process effectively combines various techniques, including SVM and kernel filtering, to enhance the accuracy and efficiency of detecting malarial parasites in blood smear images.

4.3. Explainable AI

Explainable AI (XAI) refers to a subset of AI where the outcomes produced by the model can be comprehended by humans (Došilović et al., 2018). This is in stark contrast to the concept of a "black box" in ML, where the reasoning behind a particular result is opaque, even to the designers of the system. This is different from a "white box" system, where the reasoning is clear to the designers but not necessarily to others. In digital pathology, AI models significantly aid diagnostic tasks. However, the challenge often lies in translating the results from technical language to clinical language. Even a small

error in this translation can have serious consequences (Goebel et al., 2018). XAI addresses this issue by making the AI's decision-making process more transparent and understandable. The objectives of XAI vary depending on the perspective of the person receiving the explanation and the purpose of their interaction with the AI technology (Pocevičiūtė et al., 2020; Evans et al., 2022). Typically, there are three main scenarios:

1. AI Developer: For the developers, XAI provides insight into how the AI model arrives at its conclusions, enabling them to refine and improve the model.
2. Pathologist: Pathologists use XAI to understand the diagnostic recommendations made by the AI, which assists them in making more informed clinical decisions.
3. Quality Assurance Specialist: In this scenario, XAI is utilized for the initial assessment of an algorithm's performance in a specific laboratory setting. It helps in adjusting or adapting the solution to local attributes. Additionally, XAI can be used to monitor performance drift over time, ensuring the ongoing accuracy and reliability of the AI system.

XAI thus plays a crucial role in enhancing the trustworthiness and usability of AI in complex fields like digital pathology, where clear and accurate interpretations are vital.

Explainability is crucial for developers in optimizing the performance of their AI models (Holzinger et al., 2019). For instance, understanding why certain predictions might be erroneous allows developers to identify and implement improvements in the model. Beyond accuracy in predictions, XAI also aids developers in analyzing the generalizability of their results. The process of data collection and preparation can be challenging and time-consuming, especially when human experts are involved in tasks like annotating images. Often, the collected data may not sufficiently cover all aspects needed for the intended application. For example, in cases where there are many classes to identify, the dataset might have too few examples for some of these classes. For physicians utilizing AI, a key goal is to identify and correct any errors in the model's output. XAI assists in this by providing a detailed understanding of the model's results, allowing for precise conclusions in various scenarios. This clarity also helps medical experts to build trust in the AI solution (Došilović et al., 2018). This trust is crucial for establishing an effective collaboration between humans and machines. However, it's important that XAI doesn't lead to overconfidence in the AI system. If an XAI model creates an unwarranted level of trust, it may hinder the critical assessment necessary for ensuring the system's reliability and accuracy. Thus, XAI algorithms must be carefully designed to encourage informed and thoughtful engagement with the AI, fostering a balanced level of trust that enhances, rather than replaces, human expertise.

5. Deep learning models

A deep neural network is a type of Artificial Neural Network (ANN) characterized by having multiple layers between the input and output layers. There are various architectures within deep learning, including deep neural networks and convolutional neural networks (CNNs), as mentioned by Khosravi et al. (2018). In traditional ML-based models, computer vision techniques are used to analyze different features of an image, such as color histograms or edges. These models identify groups of pixels that could be part of an object based on these features. In contrast, deep learning-based models, particularly those using CNNs, operate on an end-to-end, unsupervised basis for object detection. In this approach, features do not need to be predefined and extracted separately. The model learns to identify and extract relevant features by itself during the training process. This capability of deep learning, especially through the use of CNNs, can be extremely beneficial in digital pathology. It allows for the precise identification of abnormalities or relevant factors within medical images. Such a tool is invaluable in pathology, where accurate detection of specific pathological features, such as tumor cells or specific types of tissue damage, is crucial for diagnosis and treatment planning. Deep learning models enhance the ability to analyze complex medical images, leading to more accurate and efficient diagnoses in digital pathology (Niazi et al., 2019).

For the analysis of digitized slides, there are specialized approaches like DeepFocus, as mentioned by Senaras et al. (2018), which are designed for automatic scanning of blurry areas in images. This method includes a re-scanning feature to enhance the quality of these images, ensuring that they are clear and detailed for accurate analysis. Additionally, tools like HistoQC, as highlighted by Janowczyk et al. (2019), are employed to assess various aspects of the images, including color, contrast, brightness, and histograms. This tool is particularly adept at identifying outliers at the cohort level, ensuring the consistency and reliability of the dataset. These methods are invaluable for the quality control of whole slide images, a critical step before these images are processed by computational pathology algorithms. Ensuring high-quality images is essential for accurate and reliable analysis in digital pathology. Such preprocessing techniques help in minimizing errors and enhancing the efficacy of subsequent AI-based analyses.

AI algorithms are currently mainly used for identifying and predicting the outcome of tumors. However, the potential of AI in clinical settings is vast, ranging from precise disease diagnosis to predicting disease progression and tailoring individual treatment plans.

Fig. 9 shows an application of Pytorch (Imambi et al., 2021) in Deep Learning. Krishnadas and Sampathila (2021) developed an algorithm of deep learning based on ResNet50 and DenseNet121 to

detect the parasitized blood cells (cells infected with malaria parasite) (Mukti and Biswas, 2019; Solano-Rojas et al., 2020; Krishnadas and Sampathila, 2021). The study demonstrated a 91.72% accuracy with the ResNet50 model and 94.43% accuracy with the DenseNet121 model. Fig. 9 displays the augmentation of normal and infected red blood cells (RBCs), where the purple areas within the RBCs are identified and classified as parasites.

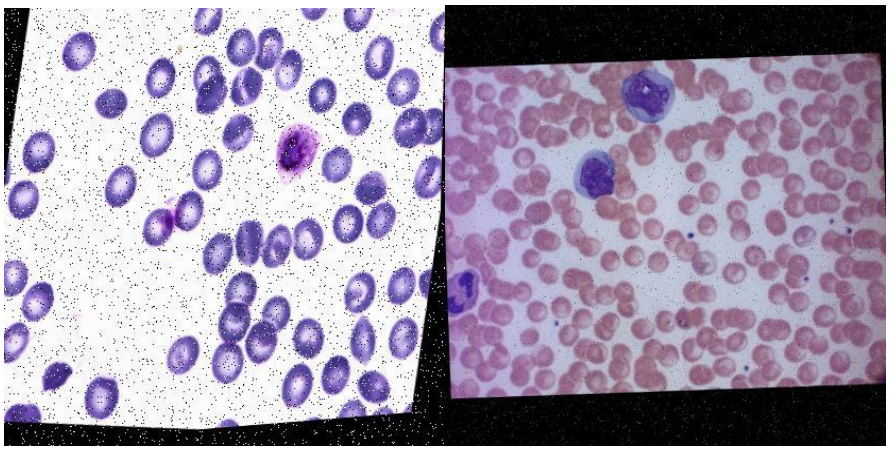

Fig. 9: Augmentation of healthy blood cells and infected blood cells (Krishnadas et al., 2021)

5.1. Examples of deep learning in digital pathology

Table 2 provides additional examples of deep learning applications in digital pathology. It is observed that deep learning methods are more frequently used in oncology-related applications than in histopathology, as indicated by the higher number of publications in the oncology field.

5.2. Transfer learning for object detection

In object detection, it's important to accurately identify multiple objects in a single image (recognition) and also pinpoint their specific locations (localization). When the task is more detailed, such as in disease diagnosis, a large and well-annotated dataset is necessary for detecting the intended targets. However, creating such a dataset for specialized applications can be challenging, time-consuming, and sometimes expensive. Additionally, updating all the weights during algorithm training can be very time-intensive. In these situations, a method called transfer learning is often used. This technique involves utilizing knowledge gained from solving one problem and applying it to a similar problem. For instance, in Digital Pathology, consider the detection of blood cells, which includes red blood cells (RBCs), white blood cells (WBCs), and platelets. RBCs might be closely packed and overlap, WBCs vary in morphology but are generally similar in shape and size, and platelets are small, making them difficult to recognize (Merino et al., 2018). Transfer learning can significantly reduce these challenges, as shown by Ren et al. (2021), where platelets are marked in blue boxes, WBCs in green, and RBCs in red. Even if the accuracy scores are not very high, a network trained through transfer learning is still capable of effectively detecting these cells (Ren et al., 2021). This approach can enhance the efficiency and accuracy of cell detection in digital pathology.

There is not much development in the field as of now as the concept is still new. It is expected that in the future, we may see more research in the field of transfer learning. Table 3 shows the transfer learning approaches conducted in Digital Pathology.

6. Challenges

As we have discussed previously, the combination of digital pathology and AI represents a significant advancement in delivering clinical results. However, there are several issues that must be resolved before these algorithms can be effectively used in clinical applications. Table 4 outlines the challenges in this field, along with proposed solutions. It's important to clarify that these proposed solutions are our suggestions and not the official or definitive answers to these challenges. Table 4 presents the challenges and potential solutions in digital pathology.

7. Conclusion

In this review paper, we have extensively examined different procedures and algorithms used in digital pathology, particularly in areas such as oncology and histopathology. These methods encompass object detection, AI, and deep neural networks. Additionally, we have addressed the current challenges faced when implementing these algorithms.

The foundation of this field primarily relies on object detection, with recent advancements being a focal point of discussion. Information gathered from sources like PubMed and articles indicates that digital pathology is more commonly applied in histopathological issues than in oncology. While progress is ongoing in the field of oncology, it may take some time to reach the same level as histopathology.

Table 2: Various deep learning techniques for cancer detection in digital pathology

Description	Reference
They employed a high-capacity deep neural network model to classify images and categorize a large number of slides into various types of cancer, such as prostate cancer and basal cell carcinoma.	(Campanella et al., 2019)
They reviewed several deep learning algorithms that use different imaging methods, such as MRI and radiodensity in CT scans, as computer-based diagnostic tools for identifying prostate cancer.	(Wildeboer et al., 2020)
They created multiple deep-learning models that can correctly classify WS images of 5 types of colorectal polyps. The overall accuracy for the classification was observed to be 93%.	(Korbar et al., 2017)
They integrated CNNs and recurrent neural networks (RNNs) to predict colorectal cancer. The deep neural network-based prediction achieved an Area Under the Curve (AUC) of 0.69. The final results indicated that deep neural networks are capable of extracting more prognostic information than human pathologists.	(Bychkov et al., 2018)
They trained various models using positive and negative sections of Whole Slide (WS) images of breast sentinel lymph nodes. Of these models, the patch model by Alake (2022) demonstrated the best performance and stability. The use of a deep learning algorithm significantly improved the accuracy of pathologists, with the AUC increasing from 0.966 to 0.995, which translates to an approximately 85% reduction in the rate of human error.	(Wang et al., 2016)
They created a smart model to distinguish between patients affected by dengue and those who are not by classifying microscopic images of blood smears. For this purpose, they used the MobileNetV2 algorithm (Sandler et al., 2018), which was pre-trained. Notable features were selected using the Relief algorithm. After processing these features, they were inputted into a SVM classifier, which achieved an accuracy of over 95%.	(Mayrose et al., 2023)

Table 3: Transfer learning experiments conducted in DP

Description	Reference
The features learned in object detection using the RCNN method (Ren et al., 2015) were applied to classify nuclei in histopathology images. Models that are not specific to any class, trained on small annotated image sections, were employed to identify nuclei. Subsequently, a Convolutional Neural Network (CNN) was utilized to group and categorize these nuclei.	(Yousefi and Nie, 2019)
A transfer learning model using both a traditional softmax classifier (Sun et al., 2020) and a SVM classifier was evaluated for classifying histopathology cancer images. This was applied to a binary breast cancer dataset and a multiclass dataset for lung and colon cancer. The SVM classifier was chosen to achieve higher accuracy in the classification.	(Fan et al., 2021)
Transfer learning in histopathology was applied to detect Acute Lymphoblastic Leukemia (ALL). In this method, a Convolutional Neural Network (CNN) algorithm was initially trained on a histopathology database for classifying different types of tissues. Then, to detect the presence of lymphoblasts, the algorithm was fine-tuned using an ALL-specific database.	(Genovese et al., 2021)

Table 4: Challenges and their solutions in digital pathology

Problem	Description	Solution
Limitations of hardware	The accuracy of digital pathology algorithms is influenced by the quantity of data accessible, and this relies on having dependable hardware and software. In some cases, the images can be quite large, up to 3 gigabytes, which necessitates sufficient storage space on both the local machine and in the cloud. Furthermore, for deep learning algorithms to accurately analyze these input images, a robust graphics processing unit (GPU) and a powerful central processing unit (CPU) are essential, as highlighted by Sze et al. (2017). When it comes to processing in the cloud, the speed can be affected by internet bandwidth limitations, as upload and download speeds are often restricted, as discussed by Liu et al. (2020).	The solutions can include more robust machines with more powerful CPUs and GPUs. For storing the images, we need bigger capacity drives and more cloud storage. Speaking of cloud storage, we need a reliable internet service for efficient data transfer.
Ethics	To utilize digital pathology techniques for disease diagnosis and prognosis, a substantial amount of clinical data is necessary. Since these methods are computer-based, they may not always be designed by pathologists but rather by data analysts, bioinformatics experts, and computer specialists. This situation can give rise to ethical concerns, as discussed by Stoeklé et al. (2018). Precision medicines can be developed more easily with the assistance of available data. However, because this data is sensitive, there is a potential for security vulnerabilities. Additionally, policies aimed at safeguarding patient personal data and privacy can restrict the access of digital pathology AI algorithms to the datasets required for training and testing, as highlighted by Chico (2018).	Currently, there is no other option than to comply with all the ethical rules that have been set.
Role interchange problems	Performing digital pathology algorithms requires not only proficient pathologists but also technical experts such as statisticians, bioinformatics specialists, and computer engineers. Pathologists formulate questions related to medicine and clinical aspects, which are then handed over to technical experts to initiate downstream industry development, as noted by Jha and Topol (2016). In the context of digital pathology, it is crucial for pathologists to possess knowledge of statistics and data analysis. This enables them to respond effectively to unexpected situations, such as the discovery of new markers or the sudden onset of diseases, by creating new analysis algorithms or enhancing existing ones, as discussed by Madabhushi and Lee (2016).	The experts need to have knowledge of the problems other than their expertise to at least some extent so that they can correctly diagnose and maybe solve the problem without calling other field experts.
Standardization	The preparation of whole slide images can encounter various issues. These problems encompass the formation of bubbles, tissue folding, and color variations, all of which can lead to unreliable data and, subsequently, incorrect outcomes, as pointed out by Hou et al. (2016). Therefore, it is essential to establish standardized procedures to minimize errors, including immediate ones like data noise, which can taint extensive datasets and result in inaccurate findings, including both false positives and false negatives. In the realm of deep learning, numerous algorithms have been developed by various developers to tackle the same tasks, as highlighted by Deng et al. (2020). To address this, there is a need to standardize the methods and employ a uniform data format. This approach enables the merging of diverse consecutive datasets from different sources into a unified algorithm, reducing variations in the process.	We need a standard worldwide accepted procedure for each of the related and similar tasks. This can be used for anything unless some other specialized procedure is needed.

ML and AI concepts are integral to digital pathology, not only for disease detection and diagnosis but also for recommending treatment options to patients based on acquired data. Deep learning, though still in development, holds significant potential for the future. CNNs, particularly transfer learning, are already being experimented with in digital pathology applications.

Furthermore, due to challenges related to role interchange, XAI is essential. This ensures that even pathologists can properly interpret and troubleshoot the models without requiring external experts, thereby avoiding delays in the workflow. In summary, this paper comprehensively explores various AI algorithms in the field of digital pathology.

Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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