

Review article

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Application and performance of artificial intelligence technology in cytopathology

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1. Introduction

Artificial Intelligence (AI) and computer science have facilitated the creation of computer-aided systems that can assist in clinical diagnostic or treatment recommendations. Computer systems built to think like people and emulate their activities, such as learning and problem solving, are referred to as artificial intelligence. There are a variety of machine learning strategies that have found success in medicine, including neural networks ([Lisboa, 2002](#page-5-0)), discriminant analysis [\(Marchevsky](#page-5-0) [et al., 2004\)](#page-5-0), classification and regression trees ([Pouliakis et al., 2015](#page-5-0)), genetic algorithms ([Saiti et al., 2009](#page-6-0)), and more recently, deep learning (Chen and Chefd'[Hotel, 2014; Xu et al., 2014](#page-5-0)). AI should be able to perform human-like abilities such as visual perception, decision-making, and communication [\(Cui and Zhang, 2021\)](#page-5-0).

In most countries, cytopathology is considered a subspecialty of pathology, despite its relative youth as a medical specialty. Studies and diagnoses of diseases are carried out at the cellular level in this field of study (free cells or small tissue fragments traditionally examined via the microscope). Papanicolaou established this field in 1928 and made it well-known when he presented the now-ubiquitous Pap test ([Chan](#page-5-0)[drasekhar and Krishnamurti, 2018](#page-5-0)). To screen for precancerous lesions on the cervix and prevent the development of cervical cancer, this test is performed ([Diamantis et al., 2014\)](#page-5-0). Cytopathology, on the other hand, does not only deal with cancers of the cervix. It was normal practice in the early days of the field to employ cytopathology to examine thyroid lesions, fluids in body cavities (peritoneal, pericardial, pleural and cerebrospinal) and nearly everybody location ([Diamantis et al., 2013](#page-5-0)). It's also possible to diagnose viral disorders and inflammatory problems using cell studies, which is not just useful for cancer diagnosis. A key advantage of cytopathology is that it does not need a biopsy or anesthesia, unlike histopathology, which necessitates a biopsy and anesthesia ([Khalbuss et al., 2011; Khurana, 2012\)](#page-5-0).

Anatomical pathology has been transformed by immunocytochemistry and supplementary molecular methods in the same way AI technologies have the potential to revolutionize cytopathology [\(Salto-Tellez](#page-6-0) [et al., 2019](#page-6-0)). It's early days for AI to be used in routine pathological practice, but recent white papers from the Digital Pathology Association (DPA) advocate that regulators and vendors collaborate to develop and implement AI technology, with the greatest goal of improving patient care ([Abels et al., 2019\)](#page-4-0).

AI is a collection of powerful machine technologies that can analyze and create meaning from large amounts of data, mimicking human skills, such as the ability visualize images, for example. Automated picture analysis is a common one in pathology, but there are others as well. AI is based on computer algorithms that analyze the picture pixels and quantitatively map them to predetermined classifications that

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indicate tissue structures or disease states. With the advent of low-cost convolutional neural networks and massively parallel computing, "deep learning" approaches can now mimic human vision and power picture recognition software. It is now able to precisely and automatically recognize tissue patterns using AI algorithms, something that has previously only been possible by pathologists and the human visual brain ([Van Eycke et al., 2018; Litjens et al., 2016\)](#page-6-0).

Neural networks (NNs) are a group of AI algorithms that has recently piqued the interest of researchers. Deep networks with several layers are represented by these intricate models, which are made up of nodes (also known as neurons). Using NNs in this manner is frequently referred to as "deep learning". High-level abstraction of input data is possible with this technology, which has remarkable performance in a wide range of applications, from image analysis to the formulation of tailored drugs ([Cuocolo et al., 2020\)](#page-5-0). Artificial neural networks (ANNs) appear to be well-suited to the fields of cytopathology and pathology in medicine, because diagnosis may only be determined by microscopic inspection by highly trained cytopathologists ([Dey, 2007; Baxt, 1995\)](#page-5-0).

Deep learning algorithms are being used in medical diagnosis in recent years. Deep learning-based image identification and counting approaches can be used to automatically identify lesions or disorders in medical pictures [\(Sato et al., 2018; Hu et al., 2019](#page-6-0)). Despite previous studies showing that AI-assisted cytology may be used to segment cytoplasm and identify cervical epithelial dysplasia [\(Bora et al., 2017;](#page-5-0) [Bao et al., 2020\)](#page-5-0), oral cancer [\(Ilhan et al., 2021](#page-5-0)), papillary carcinoma on the thyroid gland [\(Sanyal et al., 2018](#page-6-0)), and reporting urine cytopathology [\(Sanghvi et al., 2019](#page-6-0)). However, the performance of AI-assisted cytology in population-based screening is still unclear.

In this regard, the present study was carried out to provide a scoping review of the role of artificial intelligence in cytopathology. To be more precise, it intends to emphasize the relevance of applications of AI algorithms to gynaecological and non-gynaecologic cytology.

2. Methods

The literature search was performed in the English literature in the PubMed, Web of Science, Scopus, Embase, and Google Scholar. Only full-text papers that could be accessed online were evaluated. The following terms were combined to identify relevant publications: artificial intelligence; cytology; machine learning; cytopathology; Image analysis.

Inclusion Criteria: We included papers focused on the use of AI in cytopathology and assessment of the diagnostic accuracy of AI for diagnosing gynaecological and non-gynaecologic cytology covering the period from January 2000 to December 2021. There were no study design limitations.

Exclusion Criteria: We excluded articles related to AI but based on case reports, conference abstracts; articles unrelated to AI; articles not published; and articles based on animal experimentation.

3. Artificial intelligence

An artificial intelligence is a discipline of computer science that focuses on the creation of artificially intelligent computers that can perform "the activities that are typically regarded to need intelligence." Machine learning, robotics, and knowledge representation are a few of the many subfields within this larger discipline [\(Murphy, 2001](#page-5-0)). For this review, the focus will be on cytopathology and machine learning in general.

AI encompasses a wide range of techniques, including those based on machine learning, in which the computer "learns" from the data it is fed to make a prediction. Artificial neural networks (ANNs) were established in the 1980s as a synthetic approximation of human brain architecture and have now evolved into a specific machine learning method known as "deep learning" ([Bera et al., 2019](#page-5-0)) (Fig. 1).

The field of AI known as "machine learning" is concerned with the

Output

MACHINE LEARNING

Digital dataset

Fig. 1. Difference between machine learning and deep learning of AI models [\(Landau and Pantanowitz, 2019](#page-5-0)).

Convolutional Neural Network

capacity of computer algorithms to learn and complete tasks on their own, without the need for external guidance. Algorithms analyze data to arrive at intelligent conclusions. After then, these algorithms put their newly acquired knowledge to use on fresh sets of data. To produce predictions or decisions, conventional machine learning requires a lot of engineering and manual involvement, which is time-consuming and error prone. It can only handle pre-prepared instructions and a limited amount of raw data. Some examples of algorithmic approaches to distinguishing between different cell types include analysing parameters such as cell shape, cytoplasm colour and nuclei to identify squamous cells. when presented with new variables that had not been incorporated into the system, classical machine learning was far less successful ([Lau](#page-5-0) [et al., 2021\)](#page-5-0).

Supervised learning, unsupervised learning, and reinforcement learning are all types of machine learning. In order to detect patterns and forecast outcomes, supervised learning employs a training data set that has been accurately tagged by an expert [\(Mani and Sabri, 2017](#page-5-0)). Unsupervised learning does not make use of a previously assembled collection of data for training. As a result, the algorithm learns from unlabelled data, which it then uses to identify and categorize the data without any human intervention [\(James and Witten, 2017; Hinton and](#page-5-0) [Sejnowski, 1999\)](#page-5-0). The most common type of machine learning in medicine is supervised learning. A considerable amount of data is often required for unsupervised learning, and the results might be difficult to decipher. For example, in the health sciences, it is difficult to adopt reinforcement learning since it needs a trial-and-error method that currently only applies to robotics, telecommunication, and game theory ([Cuocolo et al., 2020; Cuocolo and Ugga, 2018; Shimizu and Nakayama,](#page-5-0) [2020\)](#page-5-0).

With advances in deep learning over the last decade or so, computer vision models relying on human-extracted features have fallen behind in terms of performance. Describing example, "deep learning" is a phrase for computer approaches for extracting feature hierarchies without the need for human input. You don't even need a labelled training set when using a "deep learning" approach; instead, the computer may "learn" the model's properties from a set of pixel data from photos of squamous cells and their corresponding diagnoses ([Hinton, 2018\)](#page-5-0). When it comes to deep learning, it's hard to tell exactly how the algorithm gets to a certain response for any given circumstance, and this might vary as the model learns with each iteration because it's a "black box"[\(Meijering, 2020;](#page-5-0) [Rahaman et al., 2020](#page-5-0)).

ANNs are the most used method for deep learning. ANNs -based deep learning is a relatively recent development in machine learning. These ANN, which take their cues from the nervous system, are multi-layered hierarchies of linked "neurons." To handle enormous amounts of data, labels are no longer necessary because of the intrinsic non-linearity of the algorithm. Rather than relying on human input, feature extraction in deep machine learning is a built-in component of the software [\(Pouliakis](#page-5-0) [et al., 2016; Chauhan and Singh, 2018\)](#page-5-0). While typical machine learning relies on a single level of abstraction, these methods use many layers of abstraction so that the algorithm may alter and adapt itself to new factors. Data sets that are both huge and unstructured lend themselves well to deep learning, and issues like picture categorization benefit greatly from its utilization. Its medicinal uses are being studied more and more ([Esteva et al., 2017; Coudray et al., 2018\)](#page-5-0).

4. The digital cytopathology

Digital imaging is used to make digital slides that imitate light microscopy in virtual microscopy (VM), also known as whole slide imaging (WSI). Using a scanner, the entire slide is digitized and saved as a file. By using a computer or digital device, VM allows researchers to see whatever they're interested in on a slide without the need for an optical microscope. Meaning that a computer monitor displays a whole slide scan for viewing purposes. Slides may be digitized at a variety of magnifications using current technology [\(Rojo et al., 2006](#page-6-0)).

The US Food and Drug Administration (FDA) has given the green light for the use of several WSI slide scanning systems in clinical settings ([Evans et al., 2018](#page-5-0)). With a resolution of 0.25 m/pixel, a scanning speed of 60 s, and a scanning capacity of 300 slides in one load, Philips IntelliSite Pathology Solution (PIPS) is the first FDA-approved Ultra-Fast Scanner [\(Bera et al., 2019](#page-5-0)). Brightfield and fluorescence slides may be stored in the Aperio AT2 DX System from Leica Biosystems [\(Cui and](#page-5-0) [Zhang, 2021](#page-5-0)).

The cytologist and the histologist engage with slides in different ways, and this must be considered while migrating to the digital realm. The cytologist analyses the cell while the histologist analyses the tissue. If we can make a comparison with architecture, the cytologist focuses on the brick and looks inside, whilst the histologist looks at the entire wall. Using the focus feature is especially critical while performing a cytological examination, since the histologist does not require this ([Gian](#page-5-0)[santi et al., 2010](#page-5-0)).

Surgeons are using WSI in surgical pathology for telepathology consultation, archiving, clinical diagnosis and educational purposes, as well as exams and consultations [\(Weinstein, 2005\)](#page-6-0). Virtual microscopy has been used in cytopathology in a few studies with modest sample sizes ([Steinberg and Ali, 2001](#page-6-0)). The use of digital cytopathology is increasingly widespread, ranging from clinical settings to intraoperative consultations to medical education to resolving the issue of a lack of pathologists in the field [\(Nishat et al., 2017](#page-5-0)). Therefore, the entire process of digital cytopathology relies on the ability to digitally capture and communicate information collected from a microscope's eyepiece. The digital imaging equipment (e.g., digital camera and WSI scanners), computers, and networks are all involved in this process ([Thrall et al.,](#page-6-0) [2011\)](#page-6-0).

It has also been utilized for quality assessment and improvement in fine needle aspiration cell analysis, as demonstrated by Telecytology ([Gifford et al., 2012](#page-5-0)). Rare and unique situations, classic examples of things of great significance, can also be archived and presented using this method. For faster image transfer between institutions and for gaining second opinions, WSI of slides might become a part of the patient's electronic medical record ([Khurana, 2012](#page-5-0)). With the use of teleconferences and images accompanied by lectures, real-time microscopy sessions may also be used in distance-based education. It may also be used for cytology proficiency testing and other types of research ([Gagnon et al., 2004; Eversole et al., 2010](#page-5-0)).

More and more research is showing that digital cytopathology is a viable diagnostic, educational, and consultative tool that might be used in the future Table 1. An evaluation of the degree of agreement between the telecytology diagnosis and the glass slide diagnostic is called a "concordance" ([Pantanowitz et al., 2009\)](#page-5-0). Concordance has improved

Table 1

Publications reporting diagnostic accuracy of digital cytopathology (GYN $=$ gynaecological and non-GYN =non gynaecological specimens).

(*continued on next page*)

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Table 1 (*continued*)

over time, as shown by this compiled research. As technology advanced and users became more comfortable with the systems they were using, improvements occurred. Only a few studies have proven diagnostic accuracy (i.e., the right telecytology diagnosis corresponding with the ultimate pathology diagnosis).

5. Artificial intelligence in cytopathology image analysis

Pathology images have been studied for decades with the goal of using machine learning to reliably identify disease states. Recent developments in computing and deep learning approaches, along with a surge in the use of WSI, have spurred a lot of interest in applying AI to pathology ([Janowczyk and Madabhushi, 2016; Tizhoosh and Pan](#page-5-0)[tanowitz, 2018\)](#page-5-0). AI algorithmic techniques have already shown to be advantageous in many circumstances since they can cut the time and effort necessary while also acting like a second reader and minimizing inter-reader variability ([Veta et al., 2014; Bhargava and Madabhushi,](#page-6-0) [2016\)](#page-6-0).

It's usual in digital pathology to do image analysis tasks like as counting cells or mitosis (classification). Identify histologic primitives before you can proceed with the rest of the assignments (e.g., nuclei, mitosis, tubules, epithelium, etc.). The spatial arrangement of nuclei in oropharyngeal [\(Lewis et al., 2014\)](#page-5-0) and breast ([Basavanhally et al., 2011\)](#page-5-0) tumors has related to outcome, however these techniques still require deep annotations (i.e., many entities recognized at different sizes) to extract features from. There is a pressing need to create effective and reliable algorithms for the examination of digital pathology pictures. In spite of the current emphasis on histology for machine learning in pathology, one of the earliest and most commercially successful AI algorithms in anatomic pathology addressed cytopathology.

Using 25 nuclear characteristics derived from thyroid FNA patients, Cochand-Priollet et al. discovered that four parameters based on nuclear shape, chromatin texture, and distribution of chromatin were useful in distinguishing between benign and malignant thyroid lesions in 2005 ([Cochand-Priollet et al., 2006](#page-5-0)).

As much as 71.1% accuracy was attained using the DNN by [Teramoto](#page-6-0) [et al. \(2017\)](#page-6-0) while classifying liquid-based lung cytology specimens. They accurately identified small cell carcinoma from non-small cell carcinoma in 85.6% of cases (adenocarcinoma or squamous cell carcinoma). Despite this, they focused on determining the subtypes of lung cancer and did not attempt to differentiate between benign and malignant instances. Given the high demand for ancillary testing to be performed on non-small cell lung carcinoma (NSCLC), cytopathologists are frequently asked to determine FNA material adequacy prior to performing molecular testing. Not surprisingly, quantitative analysis of cellularity in digitized cell block material has been shown to be more reliable using software than visual estimation by cytopathologists ([McDermott et al., 2016](#page-5-0)). Although a commercial machine learning algorithm (TissueMark, Philips, Amsterdam, the Netherlands) has been developed and validated for automating tumour analysis (ie, for automated tumour annotation and percentage tumour nuclei measurement in NSCLC) in formalin-fixed paraffin embedded tissue sections, the use of similar AI tools has not yet been widely applied to cytology samples ([Landau and Pantanowitz, 2019\)](#page-5-0).

According to [Momeni-Boroujeni et al. \(2017\)](#page-5-0), their neural network model for pancreatic FNA was 83.9% accurate when derived from nuclear morphometry data. In addition, they tested their model in a unique approach on "atypical" instances. Since "atypical" pancreatic FNA cases often do not progress to surgical resection, they used time since a patient has been alive and without a diagnosis of pancreatic cancer as a proxy marker of malignancy during the FNA. According to the model, there was a statistically significant difference in the median time to death or the detection of pancreatic cancer between those categorized as benign and those tagged as malignant.

This study used convolutional neural networks (CNNs) to classify cervical cytology images into five diagnostic categories, including negative for intraepithelial lesion or malignancy, atypical squamous cells of undetermined significance, low-grading squamous intraepithelial lesion and atypical squamous cells cannot exclude how-grade squamous intraepithelial lesion, and achieved accuracy of 5% ([Martin](#page-5-0) [et al., 2018\)](#page-5-0). Another cytopathology study categorized urine cytology WSI using the Paris System for Pee Cytopathology's morphometric algorithm and semantic segmentation network with a sensitivity of 77% and a false-positive rate of 31% ([Vaickus et al., 2019\)](#page-6-0).

6. . Applications of artificial intelligence in cytopathology

Recently, deep learning–based algorithms have been used for a large number of medical image-analysis applications, with levels of performance even surpassing human experts in certain tasks [\(Momeni-Bor](#page-5-0)[oujeni et al., 2017; Estava et al., 2017; LeCun et al., 2015\)](#page-5-0).

It is challenging for machine learning algorithms to discriminate between cells that are clustered or overlapped in cervical cytopathology. Deep learning techniques have been used in several research to try to picture segmentation for the analysis of nuclei and cytoplasm independently. Using three primary steps of cell identification, cytoplasm segmentation, and boundary refinement, researchers have recently discovered a deep convoluted neural network-based technique that performs better at segmenting overlapping cells in cervical cytology specimens, a common problem in cytopathology [\(Wan et al., 2019](#page-6-0)). [Pouliakis et al. \(2014\)](#page-5-0) used nuclear morphometry parameters to classify endometrial liquid-based cytology cases. To test their model for malignancy, the researchers used endometrial curettage and/or hysterectomy as the gold standard and found that it had a specificity of 90%. Several artificial intelligence algorithms in urine cytology have shown superior results to human review over the course of their long history ([Sanghvi](#page-6-0) [et al., 2019; Vriesema et al., 2000](#page-6-0)). [Table 2](#page-4-0) summarizes the application of AI in gynaecological and non-gynaecological cytopathology in this section.

7. Conclusions

In this article, we have summarized the significant advancements that have been made in the field of artificial intelligence applications to cytopathology. This review discusses cytology-specific challenges, including the need to implement digital cytology prior to AI and the accuracy of digital cytology in different studies. In addition, AI will likely play a role in cytology practice in the future, applying this technology to cytology poses a unique set of challenges. In this work we show that the application of artificial intelligence in gynaecological and non-gynaecological cytopathology in different works. As part of this review, the necessity to deploy digital cytology before AI is discussed. AI may have a role in cytology in the future but doing so will provide a unique set of obstacles. That artificial intelligence can be used in both women's health and non-health women's cytopathology is demonstrated here.

We may infer from the foregoing that AI technologies make life easier for humans, and that in the not-too-distant future, AI technologies may give a competitive edge. Artificial Intelligence may lower the amount of manual work required, and by replacing humans with machines, humans can take on other tasks. Decisions are made by the machine based on past data. Algorithms lessen the risk of human mistake. Artificial intelligence has the potential to revolutionize early illness detection research and, in turn, healthcare practice. While AI has

Table 2

The application of artificial intelligence in gynaecological and non-gynaecological cytopathology.

the potential to revolutionize medicine, many of its practical applications are still in their infancy and require further investigation and development. In order to effectively serve the public, medical professionals must also be aware of and adapt to these new technologies. Deep learning is now being used to tackle ever-more-specialized problems in the medical field. Algorithm help has been shown in several studies to enhance diagnostic sensitivity and accuracy while also reducing turnaround time. This new era of AI-augmented practice has an equal number of disadvantages. Nonetheless, this powerful technology creates a novel set of ethical challenges that must be identified and mitigated since AI technology has tremendous capability to threaten patient preference, safety, and privacy. Although AI has made great strides in the healthcare sector, present regulation and ethical requirements are behind the times. Some efforts have been made to participate in these ethical discussions, but among the medical profession, there is still a lack of awareness of the ethical complications that nascent AI technology can pose. Physicians' perspectives will be especially valuable in this debate, as they will almost certainly be working with AI in the future. Many doctors in training and in practice are concerned about the decreased number of career options due to the rising use of technology. In terms of logic and analysis, robots may be able to translate human behaviour; nevertheless, many human characteristics, such as critical thinking, interpersonal and communication skills as well as emotional intelligence and creativity, cannot be perfected by machines. In addition, Interdisciplinary research is essential for the adoption of these methodologies, and this might lead to new

studies in the future. After all, even though there were many hurdles and difficulties, the potential of application of Artificial intelligence in cytopathology which will change and improve the current health care system is promising and exciting.

CRediT authorship contribution statement

Aziza R. Alrafiah: Conceptualization, Methodology, Software, Data curation, Writing – original draft, Visualization, Investigation, Supervision, Software, Validation, Writing – review & editing.

Data availability

No data was used for the research described in the article.

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