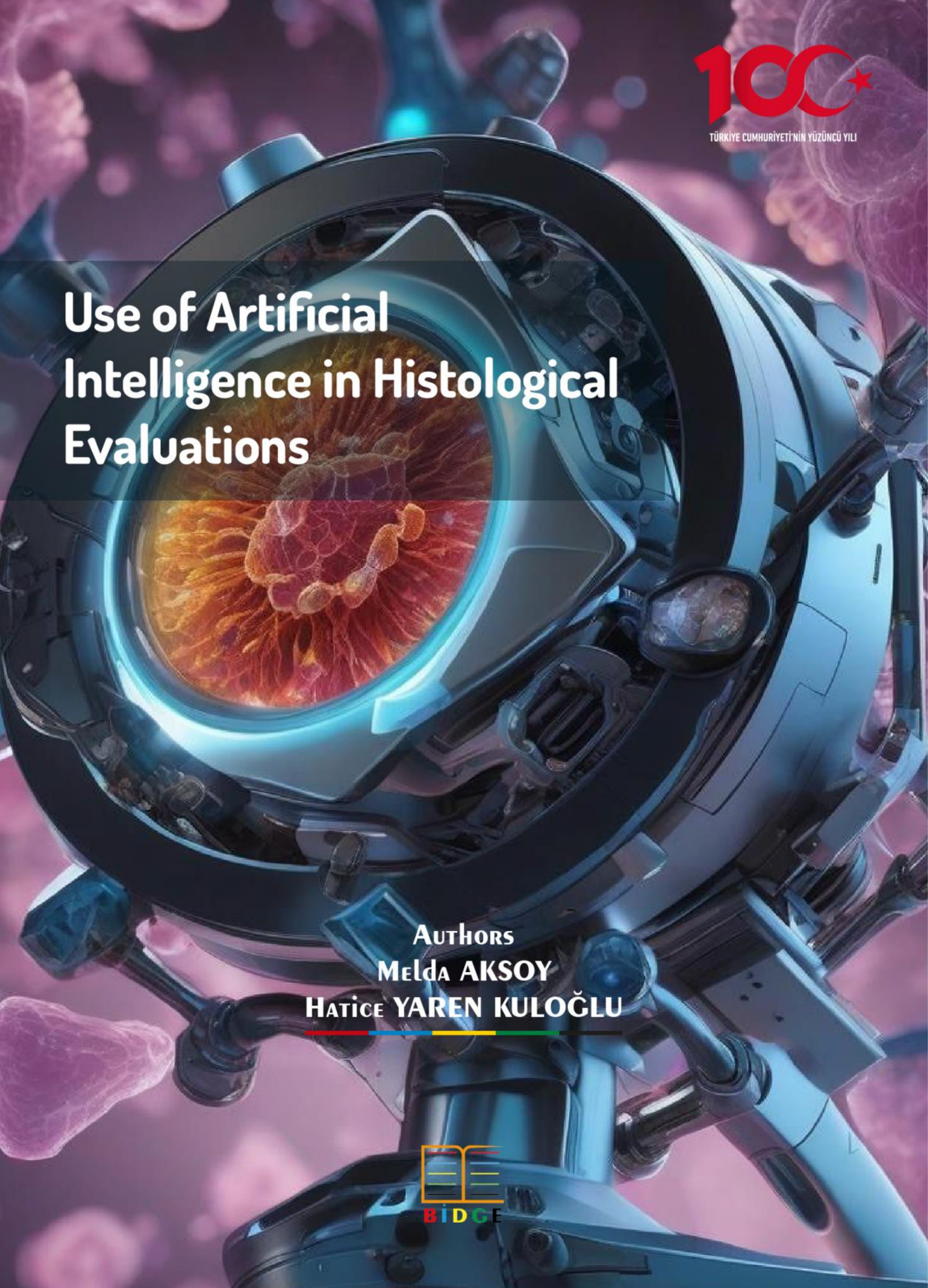

TÜRKİYE CUMHURİYETİ'NİN YÜZÜNCÜ YILI

# Use of Artificial Intelligence in Histological Evaluations


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**BIDGE Publications**

Use of Artificial Intelligence in Histological Evaluations

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ISBN: 978-625-372-300-2

Page Layout: Gözde YÜCEL

1st Edition:

Publication Date: 25.09.2024

BIDGE Publications,



Certificate No: 71374



www.bidgeyayinlari.com.tr - bidgeyayinlari@gmail.com

Krc Bilişim Ticaret ve Organizasyon Ltd. Şti.

Güzeltepe Mahallesi Abidin Daver Sokak Sefer Apartmanı No: 7/9 Çankaya / Ankara

# Content

# 1.INTRODUCTION

## 1.1.ARTIFICIAL INTELLIGENCE

Artificial intelligence is an crucial branch of science for today's technology, both for its wide range of applications and its potential to create thinking devices. The idea of creating models that can make human-like decisions has a long history for humanity. Over time, the concept of modeling the human brain with different thought structures has been applied in practice. Artificial intelligence imitates human intelligence, including thought processes, learning, and decision-making abilities, and models these capabilities in machines.

The logic of artificial intelligence encompasses a range of concepts, including intelligence, classical logic, intuition, algorithms, optimization, and learning. In order to understand what artificial intelligence is, these concepts must first be defined. Then, the basic principles of artificial intelligence can be understood more clearly, as the basis of artificial intelligence is built on imitating the human brain.

According to Edward Fredkin, the general goal of artificial intelligence research is to model the operational principles of the human brain and to make groundbreaking developments at every stage of science by using these models. Fredkin emphasizes the importance of the artificial intelligence in history and sees the emergence of artificial intelligence as equivalent to historically significant events such as the formation of the universe and the origin of life. This indicates that artificial intelligence is potentially a major turning point for humanity and it can have a revolutionary impact in scientific, technological and social terms.

The reason why Edward Fredkin sees artificial intelligence as highly significant is that he has an understanding of its current advancements and its potential future impact. However, in order to understand the concept of artificial intelligence, it is important to first define what "artificial intelligence" is. Today, although many people are not aware of it, artificial intelligence is used effectively in almost every area of social life.

Artificial intelligence is generally defined as the ability of a computer or computer-controlled machine to perform higher-level mental processes associated with the human mind. These processes include human-specific qualities such as reasoning, inferring, generalizing and learning from past experiences. The subject is quite comprehensive, and even scientists strive to reach a consensus on a unified definition.

These definitions highlight the complexity and importance of artificial intelligence. Artificial intelligence will play an increasingly crucial role in technology and society in the future, making it essential to understand and guide developments in this field. (Internet, Technological developments, http://teknolojik gelişmeler.net A.D.: June 2014).

## 1.2. History in Healthcare

The history of Artificial Intelligence goes back a long way, some say even to Aristotle. Documents attributed to Aristotle state that he tried to write the algorithm of thought but encountered difficulties in this regard. However, the real emergence of artificial intelligence is associated with the construction of the first computers and the beginning of computer software during World War II. During this period, Alan Turing, who is considered the father of computer software, introduced the idea of machine intelligence and even addressed what can be defined as intelligent in terms of thought with a test known today as the Turing Test. (Turing et al. 1950)

Alan Turing proposed the Turing Test as a means to determine what can be considered intelligent in artificial intelligence. In this test, a computer interacts with a user through a keyboard and screen, and he suggested that if the computer can give human-like responses, then that computer should be considered "intelligent". However, today's computers still have not passed this test. (http://en.wikipedia.org/wiki/Turing_test 31.09.2007)

Even if computers pass this test in the future, whether they are truly intelligent will continue to be debated from a philosophical perspective. Therefore, since its emergence, artificial intelligence has become a multidisciplinary field that intersects with many fields such as philosophy, psychology, linguistics, neurology, mathematics, robotics and computer technologies.

The term "Artificial Intelligence" was first used by Marvin Minsky and John McCarthy at a Machine Intelligence conference in the USA in 1956 (Allahverdi et al. 2002). Since then, it has been the subject of thousands of academic publications, research projects, and doctoral theses, particularly in applications such as computer hardware and software, visual recognition, pattern recognition, speech detection in robots, learning, cognitive modeling, information retrieval, information search, and game theory.

### 1.3. Case Diagnosis and Disease Diagnosis

One of the most important application areas of artificial intelligence has been Expert Systems (ES). Expert systems are computer programs designed to realize the expertise of a specialist in a computer environment. Architecturally, the most important feature that distinguishes expert systems from other decision support systems is the “Knowledge Base” and inference mechanism in ESs. In addition, when queried, ESs can make explanations with methods called forward chaining and backward chaining. Many expert systems have been developed with the artificial intelligence programming languages LISP and PROLOG. In contrast to the algorithm and data structure in traditional programming languages, artificial intelligence languages work with a knowledge base consisting of descriptive and symbolic rules and relationships, and inference mechanism. Compared to traditional programming languages, artificial intelligence languages can work with uncertain data and provide uncertain outputs. Today, expert systems can also be developed in traditional languages such as Pascal, C, C++. The development process of expert systems requires the collaboration of at least one expert and one knowledge engineer. When the system works, it can test and explain the given hypotheses, and also propose new ones.

Expert systems are used in a wide range of applications, from medical diagnosis and treatment planning to problem solving in education, from planning and data analysis to automation in industry, and from interface development and debugging in computer systems (Allahverdi et al. 2002).

The strengths of expert systems include:

a) disseminating expertise,

b) reducing costs,

c) increasing quality,

d) relying on logical cause-effect relationships,

e) working with uncertain data and rules,

f) providing explanations when questioned,

g) generating suggestions,

h) being reliable,

ı) being usable in education,

i) being able to store institutional information.

However, there are obstacles to developing expert systems and weaknesses of expert systems:

a) Lack of sufficient expert knowledge,

b) Difficulty in obtaining information from experts,

c) Experts not knowing cause-effect relationships,

d) Differences in ideas and terminology among experts on the same subject,

e) the inability of expert systems to learn and renew themselves,

f) Experts can be creative while expert systems remain static and limited,

g) high cost of development.

In the 1980s, hundreds of expert systems were developed in Japan in a process known as the 5th Generation Computers Project. These systems achieved partial success in some narrowly-defined areas of expertise, but were inadequate in performing tasks such as vision, handwriting reading, face recognition, speech recognition and understanding in robots. The project ended with great disappointment in the late 1980s.

Expanding expertise in the field of medicine has been an important factor in the development of expert systems. MYCIN, the first medical expert system developed at Stanford University in the 1970s for the diagnosis and treatment of bacterial infectious diseases, especially meningitis, is the best-known example in this field. Another important reason for the development of the system is the goal of reducing the overuse of antibiotics.

MYCIN takes inputs such as patient records, laboratory results and symptom queries and performs functions such as diagnosis, prescribing and treatment planning. The system consists of between 400 and 700 rules. Here are two example MYCIN rules:

- MYCIN Rule 035: IF the organism is 1) gram-negative AND 2) rod-shaped AND 3) anaerobic, THEN the organism is a Bacteroides with a confidence level of 0.6.

• MYCIN Rule 037: IF the organism is 1) gram-positive AND 2) cocci-shaped AND 3) grows in chains, THEN the organism is a Streptococcus with a confidence level of 0.7.

MYCIN can work interactively with the user in natural language (English) and provide explanations when needed. When reaching a diagnosis, it tries all the rules and presents them to the user when it finds a suitable rule. It can also back chain to explain a diagnosis, explaining which rules it used to reach that conclusion. When the system is asked why it did not use a rule, it can provide an explanation in the same way. (Buchanan and Shortliffe, 2007)

## 1.4. Artificial Intelligence and Digital Histology

The digitalization of diagnostic imaging applications began with the development of digital radiology, replacing X-ray films with digital images. The first adaptation of this digitalization innovation to histopathology was in 1986. It was achieved by converting a section on a glass slide visualized with a traditional light microscope or epifluorescence microscope into a high-resolution image, transferring it to a computer screen at a different location and enabling examination. Remote visualization of these high-resolution images is called digital histopathology or virtual microscopy, which includes telepathology and whole-slide imaging.

Telepathology is a remote pathology application that facilitates the transfer of image-rich histopathology data between distant computers using telecommunications technology. This method makes histopathology services more accessible by allowing histopathologists to diagnose and provide consultations remotely (Weinstein et al., 2009)

Although initially at a relatively low resolution, this technology has enabled live consultations and remote diagnosis of frozen sections. (Baak et al., 2000)

In the last two decades, the introduction of affordable digital cameras has made it possible to efficiently capture high-resolution digital images. In the past decade, digital slide scanners have been introduced and have started to replace traditional microscopes, becoming widely accepted as a "digital age" alternative in histology laboratories. These scanners typically take glass slides as input and produce whole slide images in a cost and time efficient manner. They also automate all intermediate steps, such as tissue localization and focus area selection.

### 1.5. Whole Slide Imaging

Whole Slide Imaging (WSI) is a technique that scans slide sections of tissue samples at large magnification, usually X200 or X400. The main purpose of this technology is to provide a simulation of any microscope on a computer screen. While telepathology involves the transmission of images during the examination, WSI requires a database accessible via the internet to upload and store the captured images. This allows for simultaneous review of digital slides and metadata by multiple users (Barisoni et al., 2013).

Although both can be used for diagnostic or educational purposes, clinical trials, and scientific research, digital histology has not yet been approved by the U.S. Food and Drug Administration for primary clinical diagnosis. In Europe, some clinical histology laboratories are fully embracing this digital approach. The final step towards a complete digital workflow in the histology laboratory, where most of the steps from sample collection to pathologist report are digital, is the integration of whole slide imaging into the normal workflow.

Especially in recent years, whole slide imaging has become more cost-effective and widely accepted in histology laboratories. The fact that these images are digital makes them portable, and a digital archive can be easily obtained. They also allow simultaneous viewing by multiple people at the same time and can be accessed from different locations over a computer network. Another advantage of whole slide imaging is that it directly facilitates the use of tissue morphometry and other automated image analysis algorithms (Baak et al., 2000).

## 1.6. Some Disadvantages

Despite all the advantages, digital slides have some disadvantages compared to traditional light microscopy. One of these disadvantages is the additional delay in the tissue preparation process, since slide scanning is usually performed by a researcher only after an archival review. As a solution to this problem, scanner manufacturers are developing new models with short scanning times to be integrated into the tissue preparation process.

Furthermore, the addition of scanning equipment as the final stage of the automated slide staining process can significantly reduce slide processing time and enable a fully digital workflow.

However, establishing a fully digital histology laboratory requires a specialized infrastructure for the storage and access of digital slides, along with other information technologies to optimize the workflow. Enterprise solutions and tiered management systems are needed to store this large amount of image data. In addition, integration with the laboratory information and management system is essential for a better user experience.

In terms of image quality, there is always a balance between file size and storage costs. Therefore, when compressing high-resolution images and saving data, there may be a compromise on image quality.

Another disadvantage may be the time it takes for a pathologist to make a diagnosis, which can be extended by up to 60% compared to traditional methods. (Yagi et al., 2012)

More importantly, most whole slide scanners capture tissue in only a single focal plane, which means that a structure that is actually three-dimensional may be displayed as two-dimensional. This can be problematic, as slides provide a topological relaxation, potentially leading to the loss of important information during the imaging process. In daily pathology practice, examples of digital slide use include remote consultation, quality control, education and scientific research. However, the suitability of digital slides for routine diagnosis and prognosis is currently being investigated.

## 1.7. Image Analysis

The increasing popularity of slide scanning in laboratories and the growing interest in the development and use of automated image analysis algorithms have led to the focus of these algorithms on tasks that are often perceived as tedious and time-consuming by laboratory technicians and on reducing the uncertainty caused by observer variability. The application areas of these algorithms include various histological analyses such as immunohistochemical staining, nuclear morphometry, mitotic figure counting and detection of metastases. Some immunohistochemical staining algorithms have been approved by the US Food and Drug Administration (FDA) and are now being used in clinical practice. (Rojo et al., 2009)

## 1.8. Examples of Worldwide Analysis

The implementation and development of technical standards can play a significant role in maximizing compliance, collaboration, safety, reproducibility, and quality. Quality management protocols regulating medical services and evidence-based medicine practices emphasize the standardization of measurement and reporting. Standardization in medicine is subject to different financial, geographical, political, demographic, and ethical constraints. Medical informatics has accelerated communication among researchers in different institutions and even around the world, making it easier to discuss and share strategies. Standardizing each of the pre-analytical, analytical, and post-analytical stages is crucial for obtaining reliable and reproducible results across various groups.

Variability between laboratories is affected by a number of factors. The implementation of digital pathology involves several elements, from the quality of glass slides to the quality of the images displayed on computer screens, which increases the demand for quality. Whole slide imaging itself requires significant standardization to ensure image quality across platforms and institutions (analytical-digital stage). What is critical here is to define objective quality metrics to replace subjective or regional/local approaches and establish stringent protocols.

## 1.9. Artificial Intelligence in Histology Laboratory

In histology, the development and application of novel artificial intelligence-based image analysis approaches are being carried out with various goals, such as improving diagnostic accuracy and identifying new biomarkers. These studies are led by computer engineers and data scientists, and researchers are the primary users of these image analysis approaches.

In clinical practice, histologists visually identify various morphological features of the specimen under examination and relate these features to the disease process to make their histological diagnoses. With extensive post-graduate training, histologists can quickly classify their observations.

In cancer, the complexity of genomic alterations can affect the course of disease and responses to treatment. Assessment of such alterations requires precise and accurate examination of a large number of features These histopathological features, when used alongside other radiological and genetic measurements, allow for more objective and multidimensional diagnoses.

AI-based approaches are an important step towards alleviating some of the challenges faced by researchers. These approaches have been observed to achieve accuracy levels similar to assessments performed by expert histologists and can improve human performance, especially when used alongside standard protocols. (Ehteshami Bejnordi et al., 2017)

Standardization of the color displayed with digital slides is crucial for the accuracy of Artificial Intelligence. Color variations in digital slides are often due to differences in staining manufacturers and products, variations in the thickness of tissue sections, differences in staining protocols, and differences in scanning characteristics. This variation has a negative impact on the diagnoses made by researchers and poses a significant obstacle to the generalization of machine learning algorithms. Therefore, failure to perform color normalization can negatively impact machine learning algorithms and Artificial Intelligence performance.

Image analysis tools can become valid and automated with greater consistency and accuracy compared to light microscopy. Computer-aided diagnostics are widely used in many clinical situations and studies, such as estrogen receptor, progesterone receptor, and HER2/neu assessments in conditions such as breast cancer, and Ki67 assessments in carcinoma tumors. The reliability of these methods requires standardization of the image acquisition step discussed earlier. The development of this standardization has facilitated image analysis and the development of new software tools to assist researchers. Thanks to these developments, the analysis of entire histological images has become automated, eliminating the need for researchers to select specific areas of interest.

Nuclear segmentation enables the extraction of high-quality features in histology and facilitates other analyses in computer-assisted pathology. Therefore, automatic nuclear segmentation is one of the most studied topics in artificial intelligence research, effectively performing a number of nuclear segmentation tasks.

Deep learning algorithms are also known for their state-of-the-art performance in the nuclear segmentation task. These algorithms estimate a probability map of nuclear and non-nuclear regions based on learned nuclear appearances and distinguish the final nuclear shapes using sophisticated methods. However, generalizing these methods to unseen datasets requires re-training and does not generalize if the training and test images belong to different organs. To overcome these problems, training nuclear segmentation methods on images from different organs is becoming more common.

Most histologists are interested in identifying a subset of cells within a specific anatomical region. Therefore, there has been increasing interest in the development of AI algorithms capable of identifying a subset of cells in a particular anatomical area.

They developed a new method to identify positive and negative tumor nuclei using Ki67 stain applied immunohistochemically in patients diagnosed with breast cancer. Other researchers in this field also made similar efforts and developed novel methods (Coudray et al., 2018)

Using transfer learning, they were able to accurately and automatically distinguish and identify areas of adenocarcinoma, squamous cell carcinoma or normal lung tissue in tumor-containing lung tissues from whole slide images obtained from The Cancer Genoma Atlas. However, registering more images in the system makes it possible to combine information from different modalities. (Chappelow et al., 2011)

## 2. CONCLUSION

Artificial intelligence provides valuable contributions in many aspects with its role in histology. First and foremost, artificial intelligence accelerates the diagnostic process and increases its sensitivity. Compared with traditional methods, the AI-supported diagnostic process yields much faster results, which allows patients to receive treatment quickly without having to wait. In addition, artificial intelligence can automatically detect and classify pathological areas in histopathological images, reducing the workload of pathologists and increasing diagnostic accuracy.

A key advantage of artificial intelligence in histology is its effectiveness in detecting rare conditions. Artificial intelligence can identify rare diseases or pathological features faster and more precisely than human pathologists, allowing for more accurate and timely diagnoses. Furthermore, Artificial intelligence can predict treatment responses through the analysis of histopathological features. This provides patients with personalized treatment options and optimizes treatment planning.

With its capabilities in big data analysis and processing, artificial intelligence enables histopathological data to be analyzed quickly and effectively. This allows scientists to gain deeper insights into the pathogenesis and prognosis of diseases. Finally, artificial intelligence is constantly fed with new data and improves over time. This enables the use of continuously improved algorithms in diagnosis and treatment processes.

Considering all these factors, artificial intelligence is becoming increasingly important in histology, contributing to more accurate diagnoses, more effective treatments and better outcomes for patients.

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