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Integration of artificial intelligence in histopathological and radiological image analysis: Enhancements in diagnostic workflow

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***Abstract*---**Aim: This review explores the integration of artificial intelligence (AI) in both histopathological and radiological image analysis, focusing on its potential to enhance diagnostic workflows and patient outcomes. Methods: We examined recent advancements in AI technologies, particularly deep learning and computational pathology (CPath), highlighting methodologies such as multiple instance learning (MIL) and graph neural networks (GNNs) for analyzing whole slide images (WSIs) and radiological imaging techniques like MRI and CT scans. The review also discusses challenges in data privacy, ethical concerns, and regulatory needs. Results: AI-driven tools have demonstrated improved accuracy in detecting diseases such as cancers by automating image analysis and enhancing image quality. Techniques like virtual staining and segmentation facilitate the quantification of morphological traits, enabling better prognostic predictions. Radiological imaging techniques integrated with AI provide crucial complementary information on anatomical abnormalities and disease progression. Despite these advancements, challenges like the need for substantial human annotation and computational resources persist. Conclusion: The future of AI in histopathology and radiology looks promising, with ongoing innovations poised to refine diagnostic capabilities and foster personalized medicine. Addressing ethical and practical concerns will be critical for the responsible implementation of AI technologies in clinical settings.

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Introduction

Medical imaging has advanced significantly thanks to artificial intelligence (AI) technologies, which are revolutionizing the diagnostic and therapeutic procedures. Machine learning algorithms are widely used in image interpretation, where they demonstrate exceptional capabilities in identifying and diagnosing a range of medical diseases based on imaging data. AI-driven technologies have shown to be especially helpful in radiology, helping medical practitioners to more quickly and accurately detect problems in X-rays, MRIs, and CT (computed tomography) scans. Large volumes of imaging data can be processed by these technologies far more quickly than by human experts, which makes early detection and prompt action possible. AI is also essential for improving image quality and reducing noise in medical imaging. Diagnostic accuracy is increased by using AI-driven image augmentation algorithms, which provide sharper and more detailed images. These developments make it possible for medical practitioners to see anatomical features and anomalies more clearly, which helps them make better decisions. AI also facilitates the integration of several imaging modalities, providing a thorough picture of a patient's condition—a critical component of customized therapy planning. AI is being used in the field of medical imaging to automate repetitive processes, freeing up healthcare professionals to focus more on patient care. Radiologists and other medical practitioners have less work to do when patterns and anomalies are quickly identified through automated image analysis. This improved efficiency improves resource optimization and cost-effectiveness in healthcare systems in addition to speeding up diagnostics.

Even with AI's potential to revolutionize medical imaging, problems including data privacy, moral dilemmas, and the need for legal frameworks still exist. In order to ensure responsible and ethical deployment as these technologies evolve, it is imperative that these challenges be addressed. Working together, data scientists, regulatory agencies, and healthcare practitioners may better utilize AI's potential in medical imaging while preserving patient confidentiality and protecting sensitive health data. Future developments in AI technology are anticipated to hone and expand their uses in medical imaging, eventually leading to better patient outcomes and a general progress in the field of healthcare diagnosis and treatment. A growing number of whole-slide images (WSIs) are being produced in clinical settings as a result of developments in scanning systems, imaging technologies, and storage solutions. These WSIs can be computationally processed through the use of deep learning and artificial intelligence (AI). Computational pathology (CPath), the automation and digitization of clinical pathology, provides more objective diagnoses and prognoses for patients and doctors, makes it easier to find new biomarkers, and improves the prediction of therapy responses [1] (Box 1). The origin of cancers with unknown primary can be ascertained [2], prostate cancer can be graded similarly to expert pathologists [3], colorectal cancer prognosis can be predicted more accurately than with conventional staging [4], and breast cancer lymph node metastases can be found

[5] with the aid of AI-assisted diagnosis and automatic classification of hematoxylin and eosin (H&E)-stained whole slide inoscopes.

By digitizing their existing archives or incorporating slide scanning into regular procedures, institutions are building up enormous collections of digital slides. Public programs like the National Cancer Institute's The Cancer Genome Atlas (TCGA) Program aid in the gathering of sizable cohorts from a range of disease models. Labs can now perform extensive investigations involving thousands of samples thanks to the dramatic decrease in computer storage costs and the growing availability of powerful processors, especially graphics processing units (GPUs). Furthermore, deep learning has evolved to become the primary algorithmic framework in the majority of CPath systems as a result of the advancements in AI and deep learning integration in CPath. From the early days of the discipline, which started with basic statistical studies of nuclear morphology in the 1960s [6,7,8], to the current goal of changing clinical pathology practice, this shows a significant evolution. Hand-crafted, human-interpretable features (HIFs) retrieved from areas of interest might provide insightful information about diagnosis and prognosis, as pioneering machine learning studies have shown [9,10,11,12]. Deep learning is now being used to scale these ideas since it can recognize and extract pertinent morphological traits from complicated input data on its own. CPath has the potential to identify new biomarkers even though its main application is in job automation, which lowers interobserver variability and eases pathologists' workloads [13]. AI, for example, may analyze tissue to uncover new morphological traits relevant to diagnosis and prognosis [15,16] and expose numerous biological events [14]. In addition to its clinical uses, CPath can help in drug development and therapy [17] by automating the identification of morphological alterations in tissue specimens exposed to drugs during preclinical and clinical trials.

There is still room for expansion for CPath in precision medicine and pathology research, notwithstanding these developments. New methods for improving CPath algorithms are being developed as a result of ongoing advancements in computer vision research. Examples of these methods include self-supervised learning (SSL) [19] and representation learning using vision transformers [18]. Furthermore, as precision medicine advances, more assays are required [20], which increases the amount of data gathered for each patient in order to incorporate it into the CPath workflow. Molecular and immunohistochemical tests are increasingly included in the diagnosis process in addition to histological analysis. This trend will be further accelerated by novel approaches like multiplex imaging [21], spatially resolved genomic tests [22], and 3D pathology [23], which will open up new possibilities for multimodal integration. Foreseeing future issues requires knowing which AI frameworks the CPath community will settle on. In addition to highlighting potential research fields devoted to creating reliable and generalizable representations of WSIs from large-scale, heterogeneous, multimodal, and privacy-preserving datasets, this review seeks to identify and summarize significant technical developments in WSI modeling.

In conclusion, the integration of artificial intelligence (AI) in medical imaging, particularly through computational pathology (CPath), holds transformative potential for enhancing diagnostic and therapeutic practices. By automating

routine tasks and improving image analysis, AI technologies enable faster, more accurate detection of diseases, such as cancers, and facilitate personalized treatment planning through detailed insights into patient conditions. Despite significant advancements, challenges related to data privacy, ethical considerations, and the need for regulatory frameworks remain critical. Addressing these issues will be essential for the responsible deployment of AI in clinical settings. As research continues and new methodologies emerge, including self-supervised learning and multiplex imaging, the future of CPath looks promising, offering opportunities for improved patient outcomes and innovative approaches in healthcare diagnostics. This review underscores the importance of collaboration among healthcare professionals, data scientists, and regulatory bodies to harness AI's full potential while safeguarding patient trust.

Computational Pathology via Deep Learning:

Deep learning in computational pathology (CPath) has made methodological advances that fall into two categories: AI-assisted tools that help pathologists and researchers, like image segmentation techniques and virtual staining methods, and predictive models for clinical outcomes, like cancer subtype classification, patient survival predictions, or identification of genetic mutations from whole slide images (WSIs).

Pre-Processing Tissue:

Histological slide digitization entails creating a pyramidal representation of the tissue through the generation of photographs at several magnifications (or resolutions), usually between ×40 (~0.25 μm per pixel) and ×5 (~2 μm per pixel). Digitalized WSIs are first processed through tissue segmentation to remove background areas before any AI algorithms are applied. This can be done using deep learning techniques (e.g., segmentation networks) or traditional image processing methods (e.g., image thresholding) (24) on digital images. Direct processing requires a lot of computing power due to the size of WSIs, which can be up to 100,000 times bigger than an ImageNet sample consisting of 256 × 256 pixels (26). Therefore, breaking up WSIs into smaller patches is a standard procedure. With the use of this patching technique, CPath frameworks can apply a divide-and-conquer method in which each patch is handled separately by a neural network, and the results are then combined to generate results at the slide or patient level. Image patches provide specific information, such as nuclear morphology, at high magnifications (e.g., ×40 or ×20); however, the model's ability to detect more general contextual patterns may be hindered by the small field of view. On the other hand, although resolution is lost, lower magnifications (such as ×10 or ×5) offer more contextual information on tissue architecture. Thus, context and resolution must be balanced for each application; for example, some cancer subtyping tasks (e.g., lung carcinoma classification) can be performed clinically accurately at ×5 magnification, while genetic mutation analysis usually requires magnifications of ×20 or higher (27).

WSIs for Multiple Instance Learning:

WSI categorization, or predicting disease-related clinical outcomes from WSIs, is one of CPath's objectives. One approach to tackle the computing difficulties caused by the large size of WSIs and the associated large number of patches is to reframe slide classification as a supervised learning activity at the patch level. In this method, each patch is processed to produce a patch embedding using a feature extractor, such as a convolutional neural network (CNN). The predictor then uses these embeddings to infer the patch labels, which can be manually annotated by pathologists for areas of interest or applied uniformly to all patches on a slide. The scores are combined to produce a WSI-level prediction following patch-level categorization. A parameterized neural network or non-parameterized techniques like majority voting, maximizing, or averaging may be used in the aggregation process. Nevertheless, there are a number of disadvantages to the patch-level supervision approach. Initially, human annotation requires a lot of work and is challenging to scale over thousands of WSIs. Furthermore, where pathologists have little prior knowledge, the meaning of a patch label may become unclear in applications like prognostication or treatment response prediction. much among the same tumor locations, intratumoral heterogeneity (16, 28) makes the annotation procedure much more difficult. Furthermore, labeling every patch in a WSI uniformly is possible if the region of interest dominates the WSI (27, 29); when just a tiny portion of the image is relevant (such lymph node metastases), this approach becomes troublesome and leads to noisy patch-level labels (30).

An alternative method for classifying WSIs is multiple instance learning (MIL) (31, 32), in which a single supervisory label is applied to a group of patches that make up the WSI, with the expectation that only a portion of these patches would match that label. The large difference between the amount of patches and supervisory labels in this architecture leads to it being commonly referred to as weakly supervised learning. The three steps of the MIL methodology are as follows: first, a feature extractor creates a low-dimensional embedding (e.g., a 1,024-dimensional embedding) for each patch; second, an aggregator gathers the patch embeddings to create a representation of the WSI; and third, a predictor maps this representation to the WSI label. In contrast to patch-level learning, the WSI-level label is applied to the aggregate set rather than to specific patches. The aggregator might be a parameterized function, like the attention mechanism, or a non-parameterized function, like maximizing or averaging patch embeddings (33). Attention-weighted sums of the patch embeddings can be easily derived in attention-based MIL (2, 30, 34), where each patch is assigned an attention score that indicates how important its embedding is in the prediction process. The ability of attention-based MIL to produce comprehensible heatmaps that support qualitative morphological assessments is a significant benefit.

However, because a WSI has a large number of patches, the whole set of patches and the network that goes with it cannot be stored in GPU memory at once, which makes joint training of the feature extractor and predictor more difficult. Pre-training the feature extractor on an auxiliary task to pre-extract patch embeddings is one such option. With this technique, the aggregator and predictor can function on patch embeddings that have already been compressed (e.g., 256 × 256 patches are about 200 times smaller when using 1,024-dimensional embeddings). Presumably, the pre-training of the feature extractor can take place

on natural picture datasets like ImageNet (26) (using ResNet, for example), on histopathological images with auxiliary tasks (36, 37, 38), or via self-supervised learning (39, 40, 41). As an alternative, memory-optimization techniques such using gradient checkpointing (43, 44) or accessing host memory (42) can make it easier for the feature extractor and predictor to train together. However, the intricacy and high computing demand of these techniques hinder their extensive application. In a different approach, a subset of WSI patches is randomly sampled during training (45, 46), with the understanding that each sample will contain pertinent data.

Model development will continue to be shaped by addressing computational constraints and modifying techniques to fit an expanding range of CPath applications. While recent benchmarks show that MIL and patch-level training perform comparably on a range of tasks (47), including tumor subtyping, we argue that MIL techniques will gain traction. This change is caused by the emergence of increasingly complex tasks (like survival prediction) that have weak training signals and are not well served by patch-level supervision. Additionally, hardware improvements will soon make it easier to jointly train the predictor, aggregator, and feature extractor with the full set of WSI patches in an easy-to-understand manner, increasing MIL's ability to absorb more contextual data.

Context-Aware Methodologies:

Approaches that were previously outlined assume that WSI patches are self-contained and do not possess any other contextual information. This viewpoint limits the ability to provide long-range context that is necessary for modeling tissue architecture (48), especially in situations when therapeutic response (49) and other outcomes cannot be predicted only by local cellular morphology. Lower magnifications may seem like an obvious fix, but they run the danger of hiding important cellular characteristics at a fine level of detail. Multiple instance learning (MIL) techniques could make use of a customized neural network to explicitly describe interactions across patch embeddings in order to overcome this restriction. This method requires the creation of a relational framework, in the form of a graph or a sequence, so that a network, such as a transformer or a graph neural network (GNN), may integrate and simulate the interactions according to the specified structure. As an alternative, patch embeddings from different magnifications can be aggregated by MIL techniques to implicitly integrate context.

Graph Neural Nets and Graph Representations:

A network (50, 51, 52) that shows interactions between various patches can be created by patch embeddings acting as nodes connected by edges. The locality concept, which states that adjacent regions are more likely to interact and should be linked as a result, is usually used to define connections (50, 51). A patch may, for example, connect to all neighboring patches or just its five nearest neighbors. The target of interest is then predicted using a GNN (53), which was created especially for learning on graph-structured data, by training it on the graph structure. Patch representations in GNNs spread along edges through neural signals, enabling nodes to share information with other nodes and change their

embeddings iteratively. A WSI embedding is then created using the combined contextualized node embeddings. GNNs are applicable to any WSI dataset, regardless of tissue size or shape, because they can handle graphs with different amounts of nodes and edges. Beyond patch-level analysis, graph-based MIL techniques can also depict nuclei as nodes and their connections as edges, creating a structure called a cell-graph (50, 54, 55, 56). Explicit cellular interactions and nuclear morphology are captured in the cell embeddings that are extracted around each nucleus, characterizing their appearance and revealing patterns of biological interaction. Similar to patch-graph techniques, GNNs are generally trained to map cell-graphs to clinical outcomes. The possibility of extremely high numbers of nuclei in a WSI (up to several million) makes scalability to broaden tissue regions difficult (57).

Transformers and Sequence Representations:

Transformers (18, 58) operate differently from GNNs in that they presume that all patches interact with one other regardless of their spatial placements. GNNs base interactions on locality. The transformer uses a process called self-attention to evaluate each patch embedding in terms of its relevance to all other patch embeddings. The set of patch embeddings is aggregated into a full global context-aware WSI embedding after numerous self-attention layers. Patch embeddings are organized as a series in the transformer framework, and each patch's spatial location within the WSI is indicated by its sequence position. Since it connects all patches, this method can be thought of as a generalization of GNNs since it encompasses more contextual information than just local connections. However, considering the quadratic relationship between the number of contacts and patches, this strategy has a significant computing overhead that makes end-to-end training with current hardware challenging. Transformers of lower complexity that reformulate or approximate patch interactions have been proposed as a way to relieve these computing demands (59, 60). Other approaches have also investigated interactions using transformer variations (62) or recurrent neural networks (36, 61). It is yet uncertain how effective transformer-based techniques are in comparison to graph-based techniques in terms of prediction accuracy, domain shift resilience, and generalization ability. Graph representations closely imitate biological system interactions and offer more control over patch interactions; on the one hand, they are useful in circumstances where interaction types are understood, such as when adhering to a localization principle. On the other hand, because transformers impose less inductive bias, network design is less constrained. Thus, transformers may be able to find novel long-range contextual biomarkers more effectively by using attention weights to learn graph connectivity.

Multiscale Illustrations:

Utilizing multiscale representations of WSIs, including ×5, ×10, and ×20, context can be incorporated utilizing late-fusion approaches instead of integrating it at a single magnification (4, 63, 64). This technology recovers concentric patches across several magnifications, or collects WSI representations from varying magnifications (e.g., by concatenation or summing) (64). Most importantly, these tactics operate regardless of the MIL framework that is being used. As an

alternative, mechanisms for learning to focus on diagnostically relevant regions can be created (65, 66, 67). This technique mimics the way pathologists examine diagnostic WSIs and optimizes computation by avoiding the processing of every patch at various magnification levels.

AI-Powered Assistive Devices: Artificial intelligence (AI)-based assistive tools that extract useful information from whole slide images (WSIs) for clinical and scientific applications have been made possible by advances in deep learning in pathology. These instruments are mainly concerned with virtual staining methods and tissue and nucleus segmentation.

Market Segmentation: Partitioning WSIs into discrete elements, like glands, tissue areas, or nuclei, is a crucial task for computational pathology (CPath). By permitting an objective and quantitative association of morphological traits with clinical outcomes, this segmentation is essential for improving clinical diagnosis. Segmentation can be divided into two categories: instance segmentation, which further assigns unique identifiers to each object, and semantic segmentation, which labels each pixel with a morphological class. Semantic segmentation has been used in situations including identifying Gleason patterns (70), histological tissues (71), and separating epithelium from stroma (68, 69). Nuclei (72) and glands (73), as well as mitotic cells (74, 75), are segmented using instances, and these boundaries are critical for quantifying histological properties from individual cells and glands.

Since most deep learning-based segmentation techniques follow a fully supervised paradigm, precise segmentation requires thorough pixel-by-pixel annotations. Fully convolutional networks (76) and U-Net (77), in which tissue image patches are processed by a convolutional neural network (CNN) encoder into spatially aware embeddings that are subsequently decoded into segmentation masks, are common architectures for semantic segmentation. There are methods to transform the results of semantic segmentation into instance segmentation by adding branches or making post-hoc changes; Mask R-CNN (78) is one prominent method. Even though these deep learning frameworks are incredibly powerful, the annotation process still requires a lot of labor and specialized knowledge. In order to mitigate this, specific annotation tools (79, 80) and human-in-the-loop interactive model correction approaches (81) have been presented. Large patches or complete WSIs with coarse labels can be processed by weakly supervised semantic segmentation techniques (70, 71), however their effectiveness is usually inferior to fully supervised techniques. Moreover, segmentation methods are being modified for multiplex imaging and immunohistochemistry (IHC) (21, 81, 82, 83).

The Virtual Staining:

Two main uses of virtual staining in CPath are stain enhancement, which normalizes and amplifies staining effects, and stain transfer, which translates pictures between staining modalities. Virtual staining is defined as algorithmic changes of image appearances. Differential WSI appearances among institutions due to differences in tissue processing and digitalization can potentially hinder deep learning performance. By addressing these biases, stain normalization enhances the robustness and performance of the model against domain shifts (84, 85). While stain-vector estimation has been used in traditional stain

normalization methods (86, 87), deep generative models can be trained to produce images that accurately reflect the staining intensity of reference datasets (88, 89, 90). By producing high-quality sections quickly, these models can also transform H&E frozen sections into more dependable H&E formalin-fixed paraffin-embedded sections (91). This improves surgical results. Transforming images across staining modalities, such as switching from H&E to IHC or multiplex images (92, 93), or from UV microscopy to H&E (94), is possible with stain transfer using deep generative models. While registered picture pairings still yield the best results, recent developments allow the use of unpaired data (95, 96), which streamlines the data collecting procedures. Although there is ongoing discussion regarding the clinical application of virtually stained images (97), it is hoped that the field of computational pathology would benefit from the rapid improvements in generative models.

CPath Interpretable:

Building trust between pathologists and AI systems requires ensuring that deep learning decisions are interpretable (98). Comprehending the pivotal regions that impact forecasts facilitates their confirmation against proficient information and supports the automated identification of target locations. The identification of morphological features in salient regions can aid in the discovery of biomarkers in research contexts. However, this interpretive process is complicated by the inherent complexity of models.

Saliency maps are produced using feature attribution techniques (99, 100, 101), such as gradient importance, which score input items according to their predictive significance. The goal of these techniques is to locate significant deep features by following them back to the input. Learned attention weights can be directly interpreted as important indicators by attention-based approaches (2, 14, 30, 34, 102). Although these techniques are mostly applied in WSI classification to provide patch-level significance scores, they can also be applied to pixel- or nucleus-level studies in cell-graph or patch classification frameworks. High significance ratings do not, however, automatically imply the presence of a class, hence qualitative assessments of area selection are required. Reformulating MIL to obtain patch-level predictions from WSI-level labels is an alternate method (103). Saliency maps at patch-level resolution might not be able to clearly identify the morphological characteristics guiding forecasts due to the qualitative character of these techniques. As a result, for thorough interpretability, quantitative morphological evaluations based on segmentation frameworks and histological feature analyses (HIFs)—which include shape, size, chromaticity, and topological descriptors—are crucial (104). In the end, clinical prediction interpretation can combine quantitative HIF analysis with qualitative saliency map insights. Typically, this approach entails building saliency maps for test pictures, training a prediction model for tasks like cancer grading, and pooling HIFs in important map locations for in-depth morphological study across WSIs or cohorts. This procedure is still flexible enough to accommodate various staining protocols and feature attribution techniques (105-107).

The Role of Radiologists

Radiologists play a pivotal role in the integration of AI into diagnostic workflows. They are crucial in validating AI-driven insights and ensuring their clinical relevance. Radiologists provide expert interpretations that guide the training and refinement of AI models, ensuring these technologies meet the high standards required for clinical application. By collaborating with AI developers, radiologists help identify the most impactful use cases and ensure the seamless integration of AI tools into clinical practice. Their expertise in anatomical and physiological imaging is essential for contextualizing AI findings within the broader clinical picture, ultimately enhancing diagnostic accuracy and patient care.

Conclusion

The integration of artificial intelligence (AI) into histopathological and radiological image analysis represents a significant advancement in the field of medical diagnostics. Through computational pathology (CPath) and advanced radiological imaging techniques, AI technologies facilitate the efficient processing and interpretation of whole slide images (WSIs) and radiological scans, enabling rapid and accurate disease detection, particularly in oncology. The automation of routine tasks allows pathologists and radiologists to focus on more complex analyses, ultimately enhancing the quality of patient care. Key innovations, including multiple instance learning (MIL) and graph neural networks (GNNs), have shown promise in managing the vast data generated by WSIs and radiological images. These methodologies improve diagnostic precision by capturing complex morphological features and contextual information that are vital for accurate prognostication. Furthermore, virtual staining techniques are addressing variations in image quality across institutions, thereby enhancing the robustness of AI models. Despite these advancements, significant challenges remain, particularly regarding data privacy and ethical considerations. Ensuring the responsible use of AI necessitates collaboration among healthcare professionals, data scientists, and regulatory bodies to develop frameworks that protect patient information while facilitating innovation. Looking ahead, continuous research and development in AI methodologies are expected to yield new applications within precision medicine. As AI technologies evolve, they will likely play an increasingly central role in improving diagnostic workflows and treatment strategies, ultimately leading to enhanced patient outcomes and a transformation in the landscape of healthcare diagnostics.

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