Hyperspectral Imaging for Computer-Aided Histopathology Diagnosis: Opportunities, Challenges, and Future Directions.

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Abstract

The utilization of computer-aided diagnosis (CAD) systems based on deep learning technologies for histopathology images analysis and cancer detection has been highly successful. However, many of these techniques make use of regular Red-Green-Blue (RGB) whole slide images, which offers only limited spectral data for precise tissue characterization, making it difficult for the model to recognize pathological features in biological tissues. This ultimately pushes RGB-based histopathology systems gradually towards an information bottleneck, given the increasing demand for higher diagnostic precision and early disease detection. In this regard, Hyperspectral imaging (HSI) can be considered as an alternative imaging method, allowing comprehensive spectral-spatial information obtained from multiple wavelength bands, thereby improving tissue analysis capabilities and disease detection. Recently, HSI have earned increased attention in computational pathology due to its capability to increase diagnostic accuracy compared to the conventional RGB imaging technology. This paper presents a review of Hyperspectral imaging in computer-aided histopathology diagnosis. The study examines the basics of hyperspectral imaging HSI, deep learning approaches in HSI, publicly available data sets, advantages of HSI in comparison to conventional RGB-based systems, and current challenges in HSI development along with possible avenues of further investigation. The review reveals that hyperspectral imaging possesses significant potential for advancing next-level digital pathology and precision diagnostic applications.

Keywords: Hyperspectral Imaging, Histopathology, Computer-Aided Diagnosis, Deep Learning, Spectral-Spatial Learning, Whole Slide Imaging, Medical Imaging, Artificial intelligence.

1. INTRODUCTION

Cancer is a range of disorders depicted by unregulated cellular growth that has the potential to infiltrate and damage normal tissues [1]. With over 100 different forms of conditions been identified, this disorder is caused by genetic mutations and environmental triggers, potentially impacting many body parts. This ultimately has profound influence on people affected, causing intense physical symptoms such as pain and exhaustion, substantial social and financial hardships due to expensive medical expenses, psychological consequences including stress and despair. The American Cancer Society [2] in 2024 estimated 200,140 new cases and 611,720 cancer deaths in the United States. Though since 1991, the mortality rate of cancer has declined, averting over 4 million deaths. This is due to awareness of effect of smoking, early detection, and improved treatments. Nonetheless this gain is threatened by rising incidence rates for several caners. Between 2015 – 2019, annual incidence rates surged by 0.6% - 1% for Pancreas, Breast, and uterine corpus cancers and by 2% - 3% for Liver, Prostrate, HPV-associated oral cancers, Kidney and melanoma. Significant inconsistencies persist, with higher mortality rates for stomach, liver and kidney cancers in Native Americans and rates for stomach, prostrate, and uterine corpus cancers double in Black people compared to white people [2]. GLOBOCAN [3] in their 2022 global cancer statistics, reported nearly 20 million new cases and 9.7 million deaths, with lung cancer being the leading and most diagnosed cause of death. The utilization of medical imaging technologies has proven to become an essential part of modern medicine, thus enabling diagnostic decisions and treatment planning. The consistent rate of growth in medical imaging utilization in modern healthcare further exemplifies the importance of medical imaging [4]. Effective therapy and prolonged survival likelihood is highly enhanced by early detection, when the disease is at a more controllable phase. This allows the implementation of less forceful and more efficient interventions, resulting in higher survival rate and improved prognosis [1]. Vigilance of first symptoms and Regular screening are key in early cancer detection, which ultimately improves patient outcomes and lessening of the overall impact of the disease. Traditional Diagnostic procedure for pathologists is both tedious and time-consuming, and more importantly, small metastases are very difficult to detect and sometimes they are missed by even experienced expert [5]. So also, the number of available radiologists in relation to the number of medical images continues to be disproportionate, thereby putting an enormous burden on the radiologist workload [6]. Studies have shown that an average radiologist now needs to interpret one image every 3-4 seconds to keep up with clinical workloads [7]. Unavoidably, with such an immense cognitive burden placed on the radiologists, delays in diagnosis and diagnostic errors often occur [8] [9]. These warrants an urgent need to integrate automated systems into the medical imaging workflow, which can improve both efficiency and accuracy of diagnosis.

In recent years, deep learning models have shown diagnostic accuracy comparable to that of human experts in narrow clinical tasks for several medical domains and imaging modalities, which includes, Histopathology Image [10] [11], computed tomography (CT) [12], magnetic resonance imaging (MRI) [13], chest and extremity X-rays [14] and dermatology images [15]. Of these modalities, Histopathology Imaging is considered the gold standard by pathologist for the diagnosis of Cancer diseases [16]. Pathological observation of the histological pattern of the smeared tissue sample is done under a microscope, and an image can be produced after the identification and classification of the malignant region if any [17]. With the rapid development of the application of these images to CAD, to help alleviate the burden and support the pathologist. Since 2015, there have been numerous publicly released datasets which include, the Camelyon [18] 2016 and 2017 by International Symposium on Biomedical Imaging (ISBI) for the Camelyon challenge to detect metastatic breast cancer in digital slide images of sentinel lymph node biopsies [19]. Also, there is the Public Cancer Genome Atlas (TCGA) which provides over 11,000 tissue slides of cancers across multiple organs. Unlike Camelyon datasets that include lesion-level annotations, TGCA predominantly provides slide-level labels together with corresponding cancer information [20].

Although both Camelyon and TGCA potentially provide a good foundation for automatic diagnosis based on deep learning, with large number of images, these datasets have just the three (3) basic channels for a colored image (RGB) with no spectrum information whatsoever to help the diagnosis in their dataset [21] [22]. Though RGB histopathology imaging is still popular, it was observed through recent research that the limited nature of the three-channel RGB imaging does not provide enough information for the diagnosis as opposed to hyperspectral imaging [23] [24]. Traditional RGB microscopy has a drawback from observer variability and procedural complexity limitations [24]. Recent digital pathology advances have fast tracked the integration of advanced imaging technologies with AI-driven analysis frameworks. Hyperspectral imaging has proved to be an innovative imaging technology that offers the possibility of circumventing such deficiencies since it is able to record both spatial and spectral information in hundreds of contiguous wavelength bands simultaneously [25]. In contrast to RGB imaging, hyperspectral imaging technology allows obtaining spectral profiles of individual pixels of tissues, which improves characterization and distinction of normal and abnormal areas [26]. Hyperspectral imaging becomes of growing interest in the field of computational pathology owing to its ability to register tissue-related spectral differences associated with composition, oxygen saturation, hemoglobin content, and metabolism [27] [28]. Recent research has proven the effectiveness of HSI in different medical applications, such as detecting tumors, diagnosing oral cancers, categorizing brain tissues, analyzing skin lesions, and aiding surgery guidance systems. In addition, the combination of HSI and deep learning methods, including 3D convolutional neural networks, spectral-spatial networks, attention-based networks, and vision transformers, has greatly enhanced automated tissue classification and disease detection tasks.

This paper presents a comprehensive review of hyperspectral imaging for computer-aided histopathology diagnosis. The major contribution of this review includes:

1. A comprehensive review of hyperspectral imaging techniques for computer-aided histopathology diagnosis,
2. A comparative analysis between RGB-based and HSI-based pathology systems,
3. A discussion of recent deep learning approaches for spectral-spatial tissue analysis,
4. Identification of current challenges and limitations associated with HSI pathology applications, and
5. Present future research directions for next-generation AI-driven digital pathology systems.

The structure of the paper is arranged as mentioned. Figure illustrations are provided afterwards.

2. FUNDAMENTALS OF HYPERSPECTRAL IMAGING

a. Principles of Hyperspectral imaging

Hyperspectral Imaging (HSI) is a cutting-edge optical imaging technology that merges the traditional methods of digital imaging and spectroscopy for acquiring both spatial and spectral data of an object of interest [28]. While the traditional RGB imaging sensors provide data in just three broad spectral bands, the hyperspectral sensors obtain hundreds of contiguous spectral bands through different parts of the electromagnetic spectrum [25]. The hyperspectral data obtained through HSI technology can be presented using a three-dimensional hyperspectral cube, where there are two spatial dimensions and one spectral dimension [29]. The spectra within each pixel within an HSI image are unique and are indicative of the energy interaction between the electromagnetic spectrum and the biochemical constituents of the tissue [30]. The spectra can offer important information concerning the tissue's absorption, reflection, fluorescence, scattering properties, oxygen saturation, water concentration, and cell structure [30]. As such, HSI is capable of detecting pathological changes that are usually hard to diagnose through RGB imaging techniques. The spectral characteristics of biological tissues depend largely on intrinsic absorbers like hemoglobin, melanin, collagen, lipids, and water molecules [28]. Diseases tend to modify the biochemical and physical structure of the tissues, thus causing spectral changes that can be monitored via hyperspectral image acquisition [31]. The spectral-spatial properties of HSI make it a powerful tool for the diagnosis and identification of cancers and tumors, as well as for computer-assisted histopathology [26]. The development of more sophisticated hyperspectral sensing systems, optical devices, and computational intelligence has contributed towards making HSI more applicable for biomedical imaging purposes [32]. Combining HSI with the use of deep learning has contributed to better performance in automated tissue classification and disease classification through the capability of extracting both spectral and morphological features simultaneously [33].

b. Spectral-Spatial Characteristics of HSI

One of the key benefits of hyperspectral imaging is the joint utilization of spatial and spectral information. While spatial information contains the shape, texture, and geometrical positioning of the constituent tissue elements, the spectral information represents the biochemical makeup of the respective tissue element [34]. The traditional RGB-based pathology images mainly depend upon spatial textures and colors. However, there are several pathologies that have similar RGB images but different spectra. Therefore, they cannot be diagnosed accurately using RGB images. The main advantage of hyperspectral imaging is that it can identify the spectral variations of pathologies despite the lack of visible differences between them [26]. Consequently, spectral-spatial methods have become one of the most active research fields in HSI processing. Some works have shown that incorporating spatial texture features along with spectral information substantially increases the effectiveness of tissue classification relative to relying on only spatial or only spectral data [35]. Such an ability has inspired researchers to design several new types of deep models for HSIs such as spectral-spatial CNNs, transformers, and attention-based approaches [36], [37]. In addition to this, spectral-spatial learning techniques mitigate the effects of tissue heterogeneity due to the acquisition of complementary data from tissue morphology and biochemistry [38]. Consequently, computer-aided diagnosis (CAD) techniques based on HSI have shown better robustness in detecting tumors, segmenting tissues, and localizing diseases.

c. Medical Applications of Hyperspectral Imaging

HSI technology has also found its way into biomedical and clinical imaging applications in recent years [30]. The potential of HSI in detecting cancerous tumors, determining the grading of cancer, guiding surgeries, and assessing margins during surgery has been proven to be promising [39]. Some studies have proven that it is possible to differentiate between disease and normal tissue using HSI technology [26]. For neurosurgeries, there have been applications of hyperspectral imaging to identify tumors and assist with surgery [40]. Specifically, Fabelo et al. [39] created a framework of HSI for intraoperative visualization to help surgeons in resecting brain tumors with the help of spectral tissue discrimination. Likewise, Halicek et al. used HSI along with machine learning for head and neck cancers detection [31]. In addition to the above, HSI has proven potential applications in dermatological conditions, gastrointestinal studies, retinal conditions, wound care, and even the diagnosis of oral cancer [30], [41]. The non-invasive aspect of HSI makes it more suitable for diagnostic and precision medical applications. HSI contributes to the improvement of histopathology

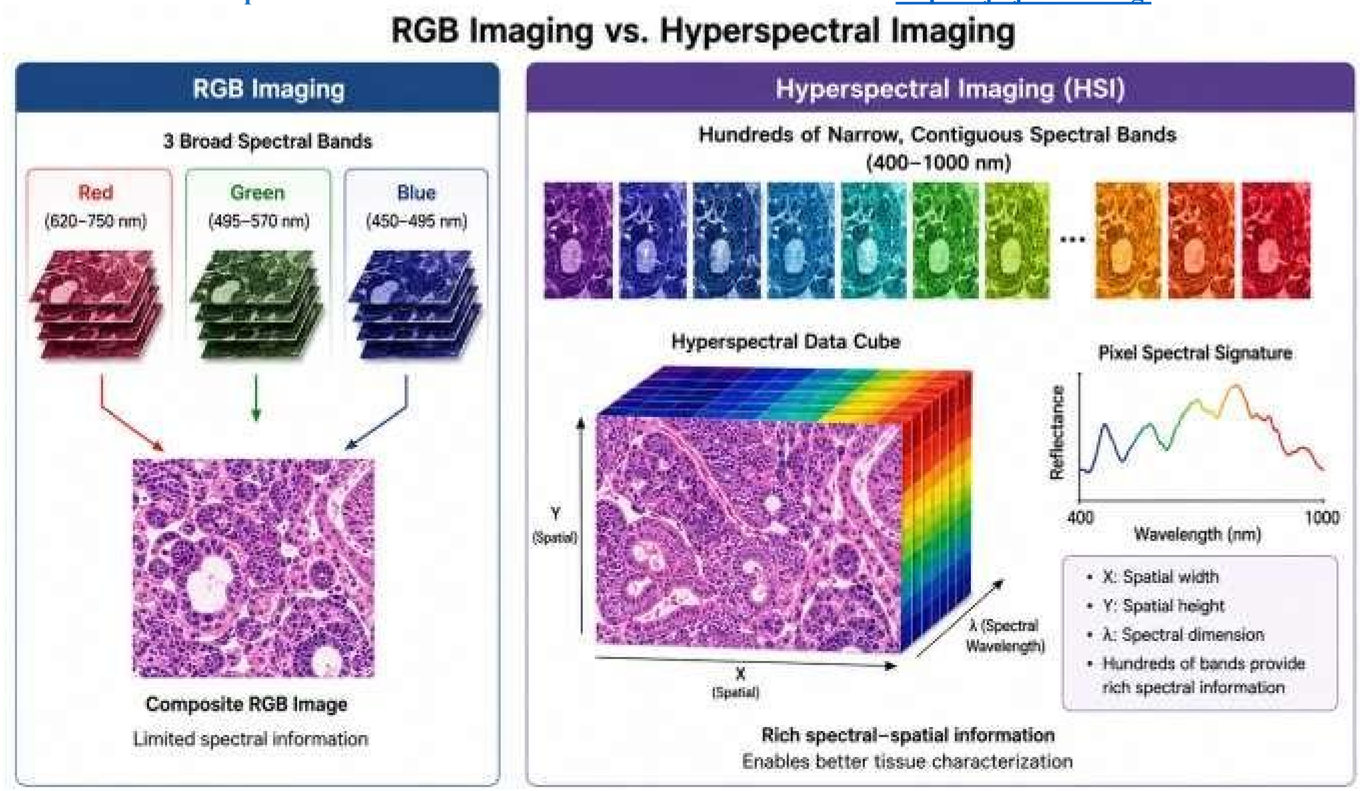

Figure 1: An overview of RGB imaging versus Hyperspectral imaging.

analysis in pathology informatics through spectral and spatial information derived from stained and unstained histological specimens [21]. As compared to conventional RGB-based pathology microscopy, hyperspectral imaging allows for additional biochemical information which can improve computer-assisted diagnostic capabilities in pathology [42].

d. RGB Imaging and Hyperspectral Imaging

Traditional RGB cameras collect data across three wide-bandwidth wavelength bands associated with red, green, and blue. Although RGB cameras offer a visual representation of the tissue structure and colors, their spectral resolution is not high enough for precise tissue analysis [21]. This problem is addressed through hyperspectral imaging, which involves acquiring a continuous spectrum for each pixel of an image from hundreds of narrow wavelength bands [25]. This technique facilitates better tissue differentiation between normal and pathological states, thereby increasing diagnostic accuracy [34]. Furthermore, RGB imaging techniques are very sensitive to the lighting conditions, staining variations, and the process of color normalization that could produce inconsistencies in automated pathology [21]. The advantage of the HSI is that it gives stronger biochemistry tissue characterization using spectral reflectance [30]. Table 1 shows a comparative outline between hyperspectral imaging and conventional RGB imaging.

HSI's capacity to detect precise spectral signatures marks a significant change of paradigm in the domain of computer-aided histopathology diagnosis. As a result, current scientific endeavors are increasingly directed toward incorporating HSI with intelligent AI frameworks in an effort to enhance the precision of disease diagnosis and tissue identification [36], [33].

3. HSI Acquisition Methodologies

The effectiveness of HSI in histopathological analysis depends on the methodologies used to collect the image as well as the approach applied in detecting the spectra [25]. This is because while the conventional imaging system can collect three broad spectra at one time, the HSI collects the spectra in hundreds of wavelength bands using special optics [30]. As such, the choice of the appropriate methodology greatly impacts the spectral resolution, acquisition rate, processing capability, and applicability in the clinical setting [32]. There are several methods applied in collecting hyperspectral imagery and some include push-broom scanning, whisk-broom scanning, snapshot imaging, and the tunable filter-based imaging systems [29], [32]. Each of these methodologies differs according to how both spatial and spectral information are acquired in the process.

a. Push-Broom Scanning Systems

Push broom scanning is another name for line scanning HSI, which is one of the most commonly used methods of obtaining HSI images in the medical field [34]. In a push broom system, the spectral data is collected in an incremental way as either the imaging sensor or object being imaged is moved within the field of vision [32]. The diffraction grating or prism is used to break down the incoming light signal into different wavelength bands, while a two-dimensional detector collects data on both the spectral and spatial dimensions at once [29]. High spectral resolution and good signal-to-noise ratio are the benefits that can be derived from push-broom systems, making them ideal for applications such as histopathology tissue analysis and microscopic imaging [30]. There are various studies that have been conducted using push-broom HSI systems for detecting tumors, classifying tissues, and guiding surgery [31], [39]. On the other hand, push-broom systems take quite some time to acquire data because of their sequential scanning process [32].

b. Whisk-Broom Scanning Systems

Point-by-point whisk-broom scanning systems collect hyperspectral measurements across both dimensions [29]. This technique entails using a scanning mirror to direct light from individual pixels to the spectrometer [32]. Whereas whisk-broom systems have very good spectral accuracy, the rate at which the image data is acquired using the whisk-broom systems is relatively slower compared to push-broom systems because individual scanning is required for every point in space [29]. The whisk-broom system is therefore rarely used in clinical settings. Whisk-broom scanners have several important strengths, including better spectral accuracy and lower optical distortion. Unfortunately, long acquisition times and increased complexity reduce their feasibility in real-world clinical environments [32].

c. Snapshot Hyperspectral Imaging Systems

Snapshot Hyperspectral Imaging technology gathers both spatial and spectral data in one exposure only [43]. This type of hyperspectral imager does not require the time-consuming process of sequentially acquiring spatial information, unlike other scanning-based systems [32]. Developments in hyperspectral imaging sensors with compact size and integration with filters have made snapshot imaging more feasible for real-time medical applications [43]. Snapshot hyperspectral imaging systems are becoming an area of interest in the field of surgery and endoscopic imaging owing to their fast-imaging process [39]. However, snapshot cameras have been known to have relatively low spectral resolution and low spatial resolution than push-broom cameras since the spectral data needs to be allocated to a few sensor elements [30]. However, recent advancements in sensor technologies and computational algorithms have significantly improved the capabilities of snapshot HSI [32].

d. Tunable Filter-Based HSI Systems

Hyperspectral imagers based on tunable filter techniques employ electronically tunable optical filters for acquiring spectral bands one after another [30]. Liquid Crystal Tunable Filters (LCTF) and Acousto-Optic Tunable Filters (AOTF) are commonly used tunable filters [32]. LCTFs work by selectively allowing specific wavelengths to pass

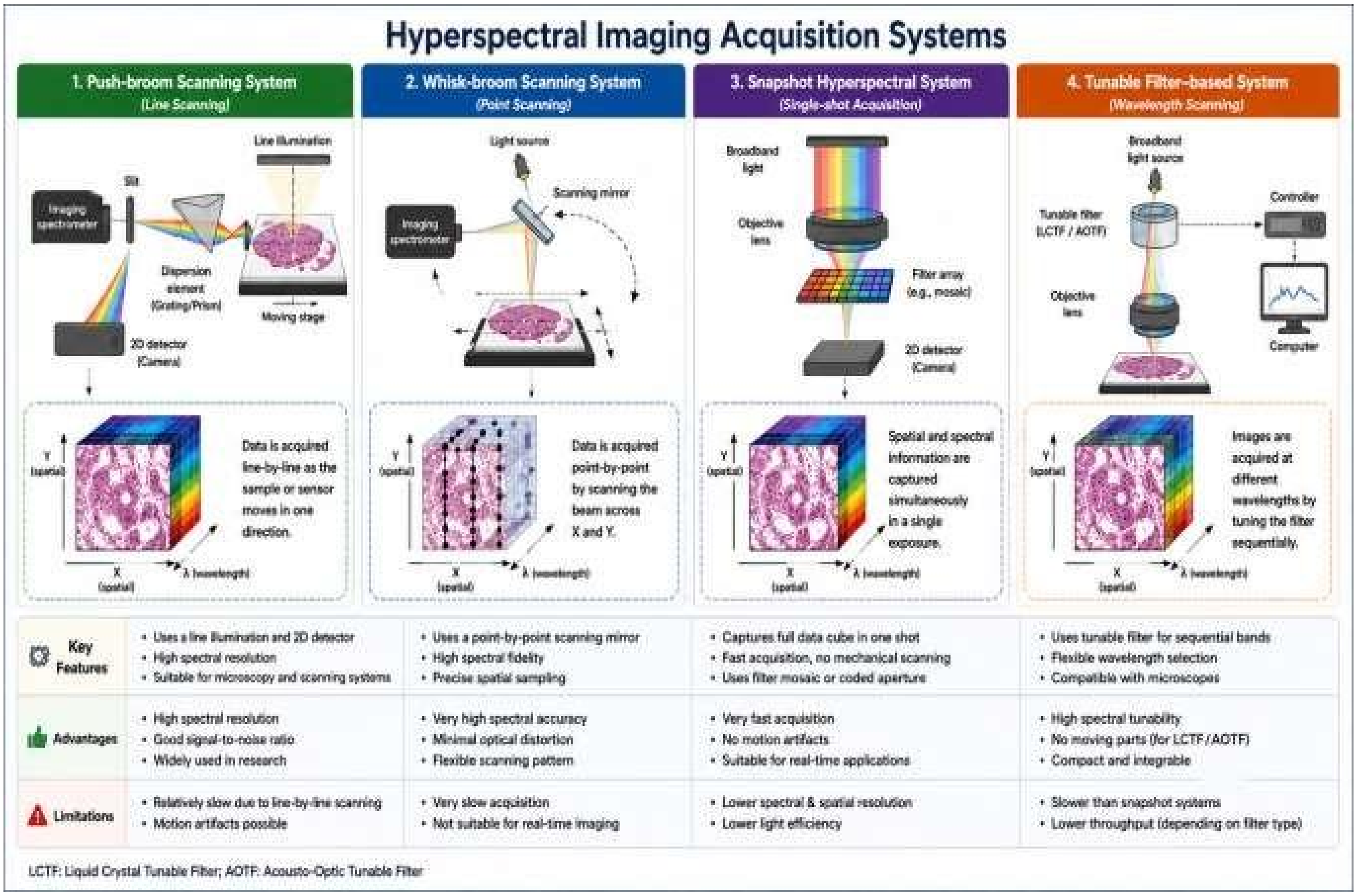

Figure 2: Overview of foremost hyperspectral imaging acquisition systems used in biomedical and histopathology applications.

through electronically controlled liquid crystals, while AOTFs use acoustic waves to modulate diffraction behavior [29]. These systems allow for programmable wavelength selection and smaller imaging system designs that can be used for microscopy-based disease diagnostics [44]. Tunable filters are especially appealing for biomedical imaging applications, owing to their compatibility with conventional optical microscopes and fluorescence imaging systems [25]. A number of histopathological investigations have adopted LCTF-based systems for tissue spectral analysis and cancer diagnostics [26]. Nevertheless, it is possible that tunable filters could exhibit diminished light transmission and slower spectral tuning rates, impacting image quality and acquisition speed [30].

e. Microscopic HSI Systems for Histopathology

Among the HSI acquisition platforms used in computational pathology, microscopic hyperspectral imaging systems are among the most significant [21]. Microscopic hyperspectral imaging systems incorporate optical microscopes and hyperspectral sensors for acquiring spectral and spatial data from either stained or unstained tissue samples [25]. When used in histopathology, microscopic HSI systems usually employ wavelengths within the visible and near-infrared range, as these spectral bands include information regarding tissue absorption and reflectance, which is useful for diagnosis [30]. Microscopic HSI systems are often employed to analyze H&E-stained samples to help differentiate between tissues and identify diseases [21]. The recent development of microscopic HSI has made it possible to conduct more accurate assessments of tumor margins, spectral classification of tissues, and biomarker analysis by incorporating it with deep learning techniques [42], [33]. Additionally, spectral microscopes with high resolution keep improving the ability of artificial intelligence-based pathology systems.

f. Calibration and Preprocessing in HSI Acquisition.

Hyperspectral image acquisition should involve appropriate calibration and processing steps to ensure that there is no spectral noise or inconsistency in the acquisition process [45]. There are several elements that might influence the quality of the spectrum [30]. White and dark references are often used during radiometric calibration in order to adjust the reflectance and balance the illumination effect [32]. Also, spectral data smoothing and denoising, for instance, Savitzky-Golay smoothing filter and wavelet denoising method, median filter, are widely used to increase spectral quality [46]. Other preprocessing techniques like spectral normalization, band selection, dimensionality reduction, and stain normalization can also enhance the robustness of CAD systems based on hyperspectral imaging technology [45]. Appropriate preprocessing techniques are necessary to improve classification accuracy, decrease computational costs, and increase generalization capacity [47]. In the continuous development of the field of hyperspectral imaging, there will be an increasing need for standard protocols of acquisition and calibration techniques [21].

4. HSI Datasets for Histopathology

Publicly available databases play a crucial role in the development and assessment of artificial intelligence-based computational pathology models [18]. Although the use of RGB histopathology techniques is supported by vast benchmark datasets, such as CAMELYON and TCGA, the number of publicly available HSI datasets is still small [48]. Almost all existing HSI datasets have been collected institutionally with a variety of instruments used to acquire images in different spectrums and calibration methods applied [32]. Available databases concentrate on oncological uses of hyperspectral imaging techniques, including head and neck cancer, brain tumors, breast cancer, and oral carcinoma. In terms of existing HSI data sets, Halicek et al. proposed a hyperspectral data set in ex-vivo for head and neck cancer diagnosis [31], while Fabelo et al. designed an in-vivo hyperspectral data set for brain tumor classification in surgery [40]. Some other studies considered microscopic HSI data sets for classifying breast tissues stained with H&E [41]. Although the results have been promising, the available HSI data sets are still relatively small and do not have adequate annotations to train deep models [46]. Furthermore, spectral variations due to differences in staining, illumination, and acquisition make deep learning even harder [30]. Lack of standardized acquisition protocols is another factor that inhibits the level of interoperability between data sets obtained using different hyperspectral imaging techniques [32]. Hence, it would be vital to conduct future research in relation to establishing larger multisite HSI databases and imaging paradigms in order to create robust clinical AI algorithms [36]. Table 2 below summarizes some representative HSI datasets and studies applied in histopathological and medical tissue analyses. Despite the current shortage of freely available HSI datasets, research on the implementation of deep learning models in the analysis of hyperspectral pathology remains challenging [46]. Therefore, further studies ought to focus on establishing standardized repositories of multicenter spectral-spatial pathological images to facilitate reproducible benchmarking and AI development [36]. Moreover, some current developments in synthetic data generation, self-supervised learning, and federated learning could be used to tackle the issue of data scarcity and labeling constraints in future HSI pathology systems [6], [49]. These techniques are anticipated to have substantial implications for the development of hyperspectral imaging frameworks in computational pathology.

5. Artificial Intelligence in Histopathology CAD Systems.

a. Traditional Machine Learning Approaches

Until the advent of deep learning approaches, CAD applications in histopathology mostly depended on hand-designed feature extraction approaches that were further processed with classical machine learning classifiers [50]. This generally included the extraction of texture, shape, color, wavelet, and morphological features in tissue images using classical machine learning algorithms like Support Vector Machine (SVM), Random Forest (RF), Decision Tree, K-Nearest Neighbor (KNN), and Naive Bayes [51]. Descriptors like GLCM, LBP, and HOG have been widely employed in tissue characterization and tumor classification problems [50]. Despite showing some level of success in pathologic image interpretation, texture-based approaches heavily relied on the quality of hand-crafted features and required domain knowledge [51]. Additionally, conventional machine learning techniques found it difficult to cope with the issue of tissue heterogeneity, variations in staining, and significant intra-class variance in histopathologic images. The introduction of hyperspectral images made the problem even more challenging for traditional feature extraction methods because of the high dimensionality of the data [45]. Machine learning models typically suffer from the decrease of their performance when working with hyperspectral data due to the curse of dimensionality and spectral redundancy [46]. This issue was solved by the usage of techniques such as PCA, ICA, and LDA in the HSI classification [29]. Despite their limitations, traditional machine learning methods established the foundational framework for automated histopathology analysis and continue to serve as baseline approaches in modern HSI classification studies [32].

b. Deep learning in Histopathology Analysis

Deep learning has played an important role in revolutionizing computational pathology through automatic feature extraction and learning from raw image inputs [52]. In many histopathology tasks, such as tissue classification, tumor grading, segmentation, metastasis detection, and localization of the diseases, CNN models have proven to be highly successful [6], [53]. The CNN-based models, including AlexNet, VGGNet, GoogLeNet, ResNet, DenseNet, EfficientNet, and Inception-V3, have demonstrated state-of-the-art results in the processing of histopathological images [53]. The availability of publicly accessible databases, such as CAMELYON16, CAMELYON17, TCGA, PANDA, and BreakHis, has also contributed significantly to advancing deep learning research. Deep learning models have several benefits compared to the machine learning techniques, including automatic feature extraction from images without the need for manual intervention in the form of feature design [52]. Moreover, the use of transfer learning has been beneficial in medical imaging due to the limited availability of labeled training datasets [6]. Moreover, Weakly Supervised Learning and Multiple Instance Learning (MIL) techniques have also received considerable attention in computational pathology due to their low dependence on laborious pixel-level labeling [54]. The potential of weakly supervised deep learning to reach clinically actionable accuracy for whole slide imaging using just slide-level labels was shown by Campanella et al. [54]. In a similar vein, Courtiol et al. developed a weakly supervised model that could localize diseases in histopathology images without demanding detailed labeling [55].Recent research has focused on developing transformer models and self-supervised learning techniques as potential solutions for pathology image analysis in place of traditional CNN-based techniques [56]. Vision Transformer models have

Table 1: Comparison between Hyperspectral Imaging and RGB Imaging

S/N	Feature	Hyperspectral Imaging	RGB Imaging
1.	Number of Spectral Bands	Hundreds	3
2.	Spectral Resolution	High	Low
3.	Spatial Information	Available	Available
4.	Spectral Information	Rich spectral-spatial data	Limited
5.	Tissue Characterization	Enhanced	Moderate
6.	Computational Requirement	High	Low
7.	Storage Requirement	High	Low
8.	Diagnostic Sensitivity	Improved	Moderate
9.	Deep Learning Capability	Spectral-spatial learning	Spatial learning
10.	Clinical Adoption	Emerging technology	Emerging technology

the advantage of capturing long-range context, and they have been shown to perform effectively in the analysis of large medical images [57]. Recent trends in pathology systems have included applying transformer models for the analysis of spectral-spatial hyperspectral images [36].

c. Deep learning approaches for Hyperspectral Imaging

The combination of deep learning techniques and hyperspectral imaging has greatly enhanced automated tissue analysis and disease classification accuracy [42]. Unlike typical RGB pathology images, hyperspectral images comprise several hundred spectral bands; therefore, it is necessary to develop dedicated models that can extract both spectral and spatial information simultaneously [25].

1. 2D Convolutional Neural Networks

One of the oldest applications of deep learning for HSIs is that of 2D CNNs. They mainly learn from the spatial information obtained either from certain bands or from reduced-dimensional hyperspectral images [58]. While being computationally more efficient, 2D CNNs do not always utilize the spectral correlation between pixels of HSI [38]. Several experiments showed that the 2D CNN architecture could produce decent classification results for hyperspectral tissues by applying spectral pre-processing methods like PCA or band selection [32]. Nevertheless, the incapacity of modeling spectral correlation is considered a significant drawback for the model.

2. 3D Convolutional Neural Networks

3D Convolutional Neural Networks have been proposed to deal with drawbacks associated with 2D CNNs and learn both spatial and spectral features from hyperspectral data cubes [38]. 3D Convolutions differ from 2D Convolutional Filters as they work in both spatial and spectral dimensions. Several recent research works have proven that 3D CNNs yield better results than traditional 2D CNNs for hyperspectral tissue classification, tumor segmentation, and disease detection applications [35]. The capability of 3D CNNs to simultaneously capture spectral continuity and spatial morphology greatly enhances the accuracy and effectiveness of classification tasks. Though 3D CNNs are often However, 3D CNNs often require large amounts of training thus computationally intensive due to the increased number of parameters [47]

Table 2: Comparative summary of publicly available Hyperspectral imaging datasets

S/N	Dataset/Study	Application Area	Spectral Range	Imaging Type	Tissue Type / Specimen	Annotation Availability	Application
1.	Halicek et. al. Dataset [31]	Head and Neck cancer	Visible–NIR	Ex-vivo tissue imaging	Surgical tissue specimens	Expert pathological annotations	CNN-based tumor classification
2.	Fabelo et. al. Dataset [40]	Brain tumor detection	Visible-NIR	Intraoperative imaging	Brain tissue during surgery	Pixel-level tumor labelling	Spectral-spatial deep learning models
3.	Breast Cancer HSI Dataset [41]	Breast Histopathology	Visible spectrum	Microscopic HSI	H&E stained breast tissue slides	Ground truth provided	Deep spectral-spatial classification
4.	Oral Cancer HSI dataset [39]	Oral squamous carcinoma	Visible-NIR	In-vivo imaging	Oral mucosal tissue	Clinical diagnostic annotations	Machine Learning and CNN frameworks
5.	Thyroid and Salivary HSI Dataset [26]	Endocrine tumor detection	Visible-NIR	Ex-vivo tissue imaging	Thyroid and Salivary gland tissues	Pathologist-verified tumor regions	Deep learning-based classification

3. Spectral-Spatial Deep Learning Models

Spectral spatial learning methods have become one of the most successful strategies for HSI data analysis, thanks to their ability to take advantage of both the biochemistry information contained in the spectra and the tissue morphology [33]. Hybrid models using 2D CNNs, 3D CNNs, attention mechanisms, and residual learning have shown impressive results for HSI pathologic analysis [35]. In this regard, Wang et al. introduced an attention-assisted spectral-spatial CNN model for hyperspectral histopathology image classification ability to capture the dependencies at a longer distance and learn contextual features [57]. Unlike conventional CNNs, which use only the local receptive fields, transformers can capture the global relationship using self-attention modules. Some recent research shows that the use of transformer models for HSI has yielded significant improvement in spectral-spatial feature extraction and in tissue classification tasks [36], [37]. Wang et al. introduced a transformer-based model for classification in medical images that can effectively learn various spectral dependencies in hyperspectral with increased tumor identification effectiveness [33]. Likewise, some modern CNN-transformer models have exhibited greater potential in spectral-spatial feature extraction and context learning tasks [55]. The addition of attention networks increases the interpretability of the model by emphasizing the diagnostic spectral bands and pathological sites [59].

d. Transformer-Based HSI Models

Transformers have recently been developed as an important area of research in the field of hyperspectral images analysis owing to their robust classification [37]. Also, Shen et al. presented a spectral-spatial transformer architecture for hyperspectral classification in medical imaging tasks [36]. SpecTr, which is a spectral transformer architecture proposed for hyperspectral pathology image segmentation, showed that transformers were an efficient method for context learning in pathology HSI [60]. The network simultaneously leveraged spatial and spectral attributes by reducing the spectral redundancy problem with sparse attention strategies [60]. Recent transformer-based works additionally incorporate spectral attention modules, multiscale feature fusion, and CNN-transformer hybrids for enhanced representation of hyperspectral imaging data [36], [37], [35]. This shows promising capabilities for next-generation computational pathology systems. While having a great performance, transformer-based methods for HSI processing encounter various issues such as high computational cost, insufficient amount of labeled images, training instability, and substantial memory usage [46], [47]. Therefore, the ongoing research aims at developing lightweight transformer networks, self-supervised spectral learning, and foundation model-based HSI solutions [6], [56].

6. Challenges and Limitations of HSI-Based Histopathology Systems

Nonetheless, despite tremendous progress that was made in hyperspectral imaging for computational pathology, several obstacles continue to persist that impede its practical implementation [45]. These include problems associated with data dimensions, complexity, availability, standardization, and clinical integration.

a. High Dimensionality and Spectral Redundancy

One of the significant problems of hyperspectral imaging is the very high dimensionality of hyperspectral data [29]. The difference between the RGB image and HSI is the number of channels in which an image is taken; while the RGB image has three channels, hyperspectral images have hundreds of channels [32]. The occurrence of spectral bands that have high correlation among themselves leads to spectral redundancy, which can lead to inefficiencies in model training and poor classification performance [46]. The effect known as the “curse of dimensionality” contributes to the overfitting of models, especially when insufficient labeled data is used for training [47]. In this regard, several techniques for dimensionality reduction like principal component analysis, linear discriminant analysis, autoencoders, and spectral band selection approaches have been suggested to simplify computations without losing discriminatory spectral data [45], [38].

b. Limited Public HSI Datasets

The absence of large-scale hyperspectral pathology datasets is one of the major challenges for the progress of HSI studies [21]. Unlike RGB pathology datasets like CAMELYON and TCGA, many hyperspectral datasets are institution-specific and obtained using customized hyperspectral imagers [40]. The lack of publicly available benchmark datasets is another limitation of deep learning in terms of replication, comparative analysis, and generalizability [46]. Besides, differences between imaging equipment, wavelengths, protocols used for capturing images, and staining methods may also create discrepancies among the datasets [32]. Current research highlights the importance of publicly available hyperspectral pathology databases that could enable proper model development and benchmarking [42], [36].

c. Annotation Complexity

The proper annotation of hyperspectral pathology images would require significant input from expert pathologists since it can be quite challenging to decode spectra manually [61]. The process of labeling pixels in huge hyperspectral cubes is very tedious and laborious, hence restricting access to quality annotated data sets [40]. Moreover, boundaries of tumors in hyperspectral images may not necessarily reflect visible RGB tissue structures, which makes the annotation process more difficult [26]. Weakly supervised learning, self-supervised learning, and multiple instance learning approaches have thus been explored to minimize dependence on annotations in HSI interpretation [6], [55].

d. Computational Complexity

The processing of hyperspectral images needs considerable computing capacity to handle storage, preprocessing, feature extraction, and training processes [47]. The deep learning models developed for hyperspectral image processing typically have complex spectral-spatial operations that consume more memory space and training time [35]. Also, Transformers-based models for HSI add to the computational complexity as the self-attention approach requires large matrix operations on both the spatial and spectral domains [36], [57]. It is therefore not surprising that lightweight approaches, model compression, and attention mechanisms are emerging research topics in medical hyperspectral image analysis [37].

e. Hardware and Acquisition Cost

In comparison to traditional RGB cameras, hyperspectral imaging systems are expensive and need high-end optical setups [25]. The hyperspectral imaging system includes special cameras, tunable filters, illumination devices, and calibration methods [32]. Additionally, the capture process for HSI can be significantly slower than the RGB capture since spectral scanning is carried out sequentially [30]. Such an issue can cause motion artifacts and limit real-time capabilities in medical applications [39]. The latest trend in the development of hyperspectral imaging is represented by snapshot spectral imaging systems and small-sized spectral sensors [32].

f. Lack of Standardization

Presently, there does not exist a widely agreed upon standard for hyperspectral imaging acquisition, preprocessing, labeling, and validation in histopathological applications [21]. The variation among spectral ranges, staining procedures, illumination, and imaging equipment has a considerable impact on data uniformity [30]. Without a standard protocol for evaluating model performance, it has become increasingly difficult to compare the performance of various HSI models and equipment [46]. It has therefore become important for modern research to establish standards for medical HSI systems [36].

g. Clinical Translation Challenges

While HSI proves to be highly promising from the point of view of research, multiple factors limit its implementation for clinical purposes [25]. Among these are regulatory issues, problems with implementing changes in the workflow, the lack of expertise among clinicians, the problem of interpretability, and deployment restrictions associated with healthcare organizations having fewer resources [59]. Integration into practice would require careful cross-validation across multi-center data sets and diverse populations to confirm reliability [54]. Therefore, explainable artificial intelligence (XAI) methods, including Grad-CAM, spectral attention visualization, and saliency maps are currently applied within HSI-powered CAD systems to improve interpretability [59]. Nevertheless, the rapid progress in AI, spectral sensing technology, and computational pathology continues to push forward the implementation of HSI for medical purposes [37].

7. Future Research Directions

Despite the great success that the use of hyperspectral imaging technology has brought to computer-aided histopathology diagnosis, there are still some aspects related to this topic that need further investigation. The progress in the development of artificial intelligence, computational pathology, and biomedical imaging provides many novel possibilities for future research and development of new spectral-spatial analysis algorithms [36], [37].

a. Vision Transformers and Foundation Models for HSI Analysis

The use of transformer structures is among the most promising lines of research for hyperspectral image processing due to its highly advantageous ability to learn from context and capture long-range correlations between spectral and spatial features [57]. While traditional deep CNNs emphasize the extraction of localized features, transformers incorporate self-attention modules to model long-range dependencies [36]. However, the recent transformer architecture proposed for HSI show improved results in terms of tissue classification and segmentation than traditional spectral-spatial CNN architecture [37]. Nevertheless, most of the current transformer models require huge, labelled data for their efficient training process [46]. The research will hence focus on exploring more computationally efficient transformers, hierarchical attention, and the integration of convolutional neural networks and transformers in future work [36]. On the other hand, the advent of foundation models and large vision-language models provides significant potential for spectral-spatial representation learning [56]. Self-supervised pre-training methods will also be vital for hyperspectral pathology systems since they minimize reliance on costly expert labeling data and enhance feature generalizability [6]. This approach will facilitate the creation of a broad range of pretrained spectral-spatial models that can be applied to different pathology applications.

b. Explainable Artificial Intelligence for HSI Systems

A significant drawback associated with the application of deep learning for computer-aided diagnosis (CAD) systems is the difficulty in interpreting the decision-making process [59]. The implementation of HSI AI systems in the clinical setting necessitates explanations that enhance physician confidence and facilitate regulatory approval [61]. Gradient-weighted class activation mapping (Grad-CAM), saliency mapping, spectral attention map (SAM), and relevance propagation are some of the Explainable AI methods that have become an integral part of hyperspectral pathology systems to ensure interpretability [59]. The latest findings indicate that through spectral attention visualization, the specific wavelength bands corresponding to malignant tissues can be diagnosed [33]. Likewise, the explainable transformer-based models allow for visualization of the spectral-spatial attention maps, helping understand how tissue classification is made [36]. Future work in the field will concentrate on creating HSI-based methods that provide clinical explanations by visualizing both spatial structure and spectral information of tissues at the same time [59].

c. Self-Supervised and Weakly Supervised Learning

The lack of large annotated hyperspectral pathology databases has been one of the primary problems constraining the development of advanced deep learning architectures [46]. The process of manually annotating hyperspectral images of tissues is extremely laborious and involves a lot of interaction with highly skilled pathologists [61]. On this account, self-supervised learning (SSL) can be considered a breakthrough for overcoming the problem of dependency on annotations in the application of machine learning to medical imaging [6]. Self-supervised learning algorithms allow deep neural networks to acquire feature representations based on unsupervised data via pretext tasks. In addition, Weakly Supervised Learning (WSL) and Multiple Instance Learning (MIL) algorithms have been investigated in computational pathology due to the fact that they do not need full pixel-level annotations but only slide-level annotations [40]. This helps to alleviate annotation difficulties, while at the same time retaining competitive classification accuracy levels. The future of SSL and MIL can be combined with the Spectral-Spatial Transformer network for building effective HSI pathology models [36].

d. Federated Learning and Privacy-Preserving AI

Security and privacy issues continue to represent major obstacles for extensive collaboration on AI-based healthcare solutions [61]. As hyperspectral pathology data is usually collected by individual organizations and hard to transfer, federated learning has recently appeared as a powerful method for collaborative training without sharing patients' information [49]. Federated learning allows healthcare organizations to collaborate and train machine learning models together without compromising patients' privacy [49]. Federated learning may have many beneficial effects on both dataset diversification and model performance. Federated learning for medical imaging and computational pathology applications has been shown to be feasible by recent research [62]. It is anticipated that future work will focus on federated learning methods using spectral-spatial learning algorithms which can incorporate HSI datasets across multiple hospitals while preserving patients' privacy and regulatory compliance. A potential synergy between federated learning, self-supervised learning, and transformers will likely spur the advancement of HSI-based diagnostic systems.

e. Multimodal and Hybrid Imaging Systems

In recent years, computational pathology research has started paying more attention to the use of multimodal learning for more accurate diagnoses and precision medicine [63]. Instead of being based on only one type of image modality, next-generation CAD systems will be multimodal and utilize complementary information from a variety of sources such as RGB images, hyperspectral imaging, radiology images, genomics, and clinical metadata [64]. RGB-HSI systems have shown good results by leveraging the strengths of both imaging modalities for more accurate diagnoses [37]. Moreover, transformers that are capable of handling spectra, spatial, radiological, and genomic data simultaneously have been receiving increasing attention in the design of future cancer diagnostics systems [63]. Such integration methods can help greatly in advancing the field of personalized medicine and precision oncology. The future, hence, is predicted to see a trend toward multi-modal integration techniques and unified foundation models.

f. Real-Time and Edge-Based HSI Systems

Real-time implementation of hyperspectral imaging systems is difficult because of the substantial computation that comes along with the spectral-spatial analysis [47]. Modern HSI devices usually depend on powerful GPUs and involve multiple preprocessing steps, restricting their implementation within a clinical setting [32]. Several innovations in the design of efficient deep learning models, model compression, and hardware acceleration have facilitated the development of edge computing solutions for HSI data analysis [36]. Miniature hyperspectral imagers and snapshot imaging systems enhance the efficiency of data acquisition and minimize motion artifacts during surgery [39]. Thus, future research can consider designing real-time HSI CAD systems that will be useful for guiding surgical operations, fast tissue screening, and pathology analysis at the point of care [40]. The use of edge-based AI systems combined with an efficient spectral-spatial model can be helpful in this regard.

8. Conclusion

Hyperspectral imaging technique is becoming more popular in the field of computer-aided histopathology diagnosis, owing to the capability of the technique to provide both spectral and spatial information regarding the tissue [25]. In contrast to conventional imaging systems which focus mainly on the structural details of the tissues, HSI is able to generate biochemical and spectral features that improve the process of tissue classification and discrimination [26], [34]. AI techniques such as deep learning, spectral-spatial convolutional neural networks, transformers, and self-supervised learning have recently revolutionized HSI-based computer-aided diagnostic systems [36], [33], [37]. However, despite all these improvements, there are still many obstacles that prevent the implementation of such HSI systems in a clinic, which include issues of high-dimensionality, inadequate benchmark datasets, difficulties with data annotation, computational power demands, non-standard acquisition protocols, and integration into clinical workflow [45], [46]. Despite these problems, research is still actively being conducted into such fields as explainable AI, federated learning, multimodal imaging, lightweight transformer models, and foundation models for hyperspectral pathology [6], [59] [49]. It is highly probable that future computational pathology systems will combine hyperspectral imaging with multimodal AI models that can utilize spectral, morphological, genomic, and clinical data in order to achieve better precision medicine [63]. Therefore, hyperspectral imaging shows great potential for revolutionizing the field of digital pathology and next-generation AI-based cancer diagnostics.

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