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Artificial intelligence in computational pathology – challenges and future directions

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ABSTRACT

The field of digital histopathology has seen incredible growth in recent years. Digital pathology is becoming a relevant tool in healthcare, industrial and research sectors to reduce the saturation of pathology departments and improve the productivity of pathologists by increasing diagnostic accuracy and reducing turnaround times. Artificial Intelligence (AI) algorithms may be used for the identification of relevant regions, extraction of features from a histological image and overall classification of images into specific classes. The combination of digital histopathology imaging and AI therefore presents a significant opportunity for the support of the pathologists' tasks and opens up a whole new world of computational analysis. In this paper, we have analysed the present, the challenges and the future of the computational pathology discussing the different existing strategies to overcome its main limitations and ensure the computational pathology acceptance. The lack of labelled data, which is the possibly largest challenge for all medical AI applications, is even more pronounced in computational pathology because of the multi-gigapixel nature of the images and high data heterogeneity. We consider the future of the computational pathology is the combination of weak label strategies with active learning and crowdsourcing scenarios since it would remove some of the workload from clinical experts and manual annotation obtaining clinically satisfactory performance with minimal annotation effort. In addition, we believe areas such as explainable AI, data fusion and secure role-based data sharing will be receiving increasing research attention in computational pathology in the close future.

1. Introduction

Pathologists play a crucial role in cancer diagnostics. The traditional work of a pathologist includes manual and visual study of tissue and bodily fluids in a microscope to diagnose illness and guide treatment. This is a time- and labour-intensive task, which relies on the expert eye of the pathologist, hours of observation, research, and collaboration with other histopathological experts. Even under optimal conditions, cancer diagnostics is a challenging task that is often associated with a relatively disappointing reproducibility among pathologists.

Unfortunately, the incidence of cancer in the western world has followed a growing trend in the latest decades, resulting in a significant amount of biopsies that need to be analysed in hospitals and clinics every year [1]. This involves logistic and staff challenges, especially as Europe also faces an increasing shortage of pathologists [2]. As a result, the high demand for cancer diagnostic tests can lead to work overload in pathology departments and important delays in diagnosis that have significant adverse impact on treatments' assignment and effectiveness. The ability to provide the patients, and their clinicians, with a precise diagnosis, an accurate determination of prognosis, and a predication of suitable therapeutic strategies may be improved by the addition of supplementary immunohistochemical and genetic analyses [3,4] - however, this again relies on the use of scarce expert pathology resources. Additionally, a significant number of early detection campaigns are being launched at several European countries, with the objective of raise awareness on the importance of prevention [5]. This is leading to an even higher number of tests deriving to pathology departments throughout Europe and in many other countries.

1.1. Increasing interest in digital and computational pathology

Digital pathology is a sub-field of pathology that focuses on scanning, interpretation, and management of digital tissue slides. *Digital slides* are created when tissue slides are scanned with a

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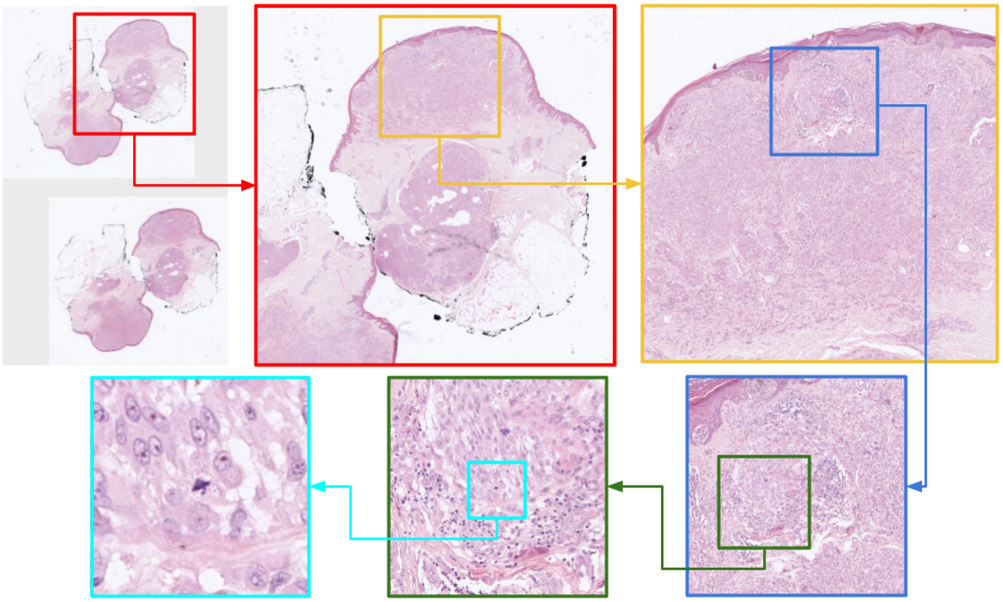

Fig. 1. Example of WSI from a skin tissue sample at different magnification scales depicted in red, yellow, blue, green and cyan regions. The maximum magnification scale lets the visualization of an atypical mitosis located at the center of the cyan region. (For interpretation of the colours in the figure(s), the reader is referred to the web version of this article.)

microscopy slide scanner and it provides high-resolution images called *Whole Slide Images* (WSIs) that can be viewed on a computer screen. WSIs are also named gigapixel images since their size is frequently of more than 10^{10} pixels so that they require large amounts of time and effort to be processed. Fig. 1 shows the aspect of a WSI at different magnification scales. Digital pathology has seen an incredible growth in recent years as the quality of microscopy scanners has increased and computational hardware has become more powerful.

Digital and *Computational pathology* are confusingly used apparently interchangeably, yet mean somewhat different things. According to the Digital Pathology Association (DPA), Digital Pathology is "*a blanket term that encompasses tools and systems to digitize pathology slides and associated meta-data, their storage, review, analysis, and enabling infrastructure*" and Computational Pathology is "*a branch of pathology that involves computational analysis of a broad array of methods to analyze patient specimens for the study of disease focused on the extraction of information from digitized pathology images in combination with their associated meta-data, typically using artificial intelligence methods such as deep learning*" [6].

The increased attention on digital and computational pathology can be recognized from activities of worldwide organizations. The US Food and Drug Administration approved the first US digital pathology system for primary diagnostic use in April 2017 [7]; the UK Life Sciences Industrial strategy reinforced actions for the use of digital pathology [8]; the Royal College of Pathologists stressed the need for investment to support digital pathology infrastructure [9]; the Innovative Medicines Initiative (IMI) launched a H2020 call focused on supporting the collaborative development of artificial intelligence in pathology in 2019 [10]; the project funded by this call started in February 2021 with the aim to create a repository of digital copies of around 3 million WSIs and a budget of 32 million euros [11]. There are also some pioneer ongoing initiatives focusing on the digitization of the histopathology departments of a few countries [12].

Digital and computational pathology are also becoming growing business areas. The global digital pathology market is projected to reach USD 1,054 million by 2025 from USD 553 million in 2020, at a CAGR of 13.8% during the forecast period [13]. The growth of digital and computational pathology is not only reflected in social and economic terms but also in academia with the recent increase in the number of publications in the field. 3.618 and 4.983 papers related to computational pathology and artificial intelligence terms were published in PubMed in the last 5 and 10 years, respectively. This means that the 72.6% of the publications are concentrated in the last 5 years. The results follow a similar trend in Google Scholar where 66.830 out of 96.830, i.e. a 69% of the papers, were published in the last 5 years. The statistics of published papers according to their year are depicted in Fig. 2. These figures demonstrate significantly the interest of the scientific community in the topic. In fact, there is a great effort in pushing forward the state of the art in the computational pathology area. For an in-depth review of artificial intelligence models for computational pathology and clinical perspectives, we refer readers to [14–16].

1.2. Computational pathology methods

The past years have seen an increase and improvement of artificial intelligence (AI) methods applied to histological imaging analysis. AI algorithms may be used for WSI normalization, identification of regions of interest (ROIs), extraction of features from a large WSI and overall classification of images into specific classes. The combination of digital histopathology imaging and AI represents as such a significant opportunity for the support of the pathologists' tasks. As seen in many computer vision and image processing applications, early attempts in computational pathology integrated expert knowledge into feature extraction design, which is known as feature handcrafting. The features are generally produced by image processing methods and thereafter feed into machine learning (ML) networks that can be trained to perform different tasks. However, recent approaches are mainly based on deep neural networks where feature extraction is an intrinsic part of the model and features are automatically learned from data, known as data-driven approaches or automatic learning. Image processing and ML-based methods with good results can be found in the literature where statistical, morphological, colour, structural and/or textural features are extracted from WSI and combined with well-known supervised classifiers (e.g., support vector machines, random forest classifiers, multi-layer perceptron, etc.) [17–19]. Some works also combine handcrafted features with deep-learning features for accuracy im-

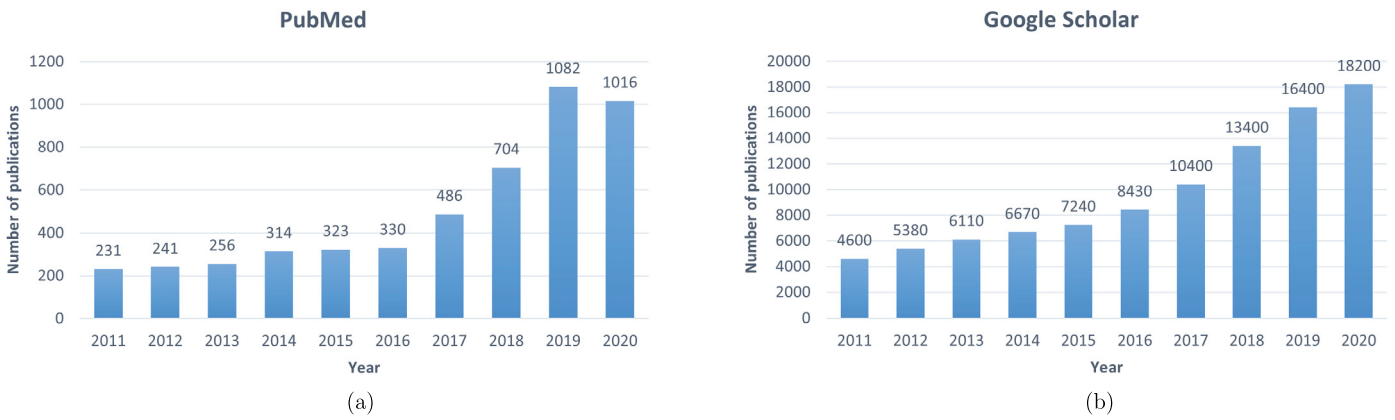

Fig. 2. Statistics of published papers using as search query "computational pathology and artificial intelligence": (a) PubMed. (b) Google Scholar.

provement [20,21]. Even when using deep neural networks and data driven approaches, the system pipeline often includes preprocessing steps based on more classical image processing [22–24]. Preprocessing might especially be useful if there is a large diversity in the data or the amount of training data is scarce. Overall, deep learning approaches usually outperform traditional ML methods [25–27] and in this paper we will focus on deep-learning approaches.

The earliest success of deep neural networks was in the task of image classification, where an image was classified to be "cat", "bird", "bicycle", etc. This was done using supervised learning with an *image-based* label, for example using the ImageNet database [28]. When supervised learning is applied to tasks like segmentation or detection of smaller structures, detailed annotations and labelling of regions in the image are needed. Such labels are called *pixel-wise* labels, or sometimes strong labels. For many computational pathology tasks, we might only have access to the image-based labels that can directly extracted from the patient's medical records such as final diagnose, grade and/or stage of disease, or follow-up information. However, learning such a class is not as direct as in the ImageNet classification of images, since the WSI are gigapixel images. A gigapixel image cannot fit into a neural network "all in one go", and has to be patched or tiled up somehow, see Subsection 2.1 for more details. In addition, there are often large areas in the image that are of no diagnostic relevance. If the regions of interest are annotated and labelled with pixel-based labels, supervised learning is straightforward. However, if only slide-based labels are available, learning models are much more challenging. See Subsection 2.3 for an overview of state-of-the-art deep learning models in computational pathology. Another important challenge lies in dealing with histological imaging variability, see Subsection 2.2 for more details.

The three aforementioned computational pathology challenges will be widely discussed in the following section. Besides, in Section 3 we will discuss some other areas that we believe will be receiving increasing research attention in computational pathology in the close future.

2. Challenges

Rising needs and challenges within the health service in general can also be applied to the pathology speciality in particular. There is a continuous increase in the demand of pathology services due to the increasing number of biopsies and cancer cases as a consequence of the longer life expectancy in Europe. Besides, novel screening processes with high sensitivity and low specificity are now being implemented in general basis [2]. More efficient prognosis in terms of time and personalization are key elements that need to be in place to improve health services in our current society.

Within that context, computational pathology is fundamental to make the pathologist's work of gathering relevant diagnostic information far more effective and accurate by combining the digitalization and the use of new AI algorithms for automated analysis support of histological images. However, the global establishment and full exploitation of this technology require serious challenges to be tackled. We will here discuss some of the particular challenges that we see within computational pathology.

2.1. Multi-gigapixel nature of images

One of the main limitations of the broad implementation of computational pathology is that it heavily depends on optimized software and powerful hardware to be able to deal with large gigapixel WSIs (around 2-3 GB per digital slide). The large size of WSI also implies significant store requirements at pathology departments and turns data transfer into a bottleneck.

Multi-gigapixel nature makes the processing of the complete WSI unfeasible. To work around this problem, the most common strategy is to follow a patch-by-patch approach, breaking the image down into smaller patches or tiles based on the annotation input or other preprocessing steps. Such patches are stored and thereafter processed sequentially, and possibly independently. Patching is used both in learning of models and prediction of previously unseen slides. The patching is in itself a time-consuming process and obviously require extra storage. An alternative workflow is to work with list of coordinates pointing to regions of interest or patch corners. For further processing and training of models such lists can be associated with several tags and used as input. Such workflow can be flexible allowing different and multiple resolution and sizes of tiles to be formed and processed on the fly. However, this alternative can represent a high computational cost by itself processing time since WSIs have to be loaded and preprocessed during training every time. The best patching option should be chosen depending on the application and hardware characteristics. Patching has the inconvenience of contextual information loss, and memory and computational constraints can make it necessary to find a trade-off between resolution and patch size. Multi-resolution analysis to integrate information from multiple scales has also been explored in the literature [29–33]. A reasonable balance between the competing demands of speed and accuracy should exist to be considered as the best strategy [34]. In recent years, attention-based models are also gaining popularity as an alternative to the traditional patch-based approaches mimicking the way the pathologist works to identify the most relevant diagnostically indicative areas and try to learn only from them. Their

goal is to reduce the number of model parameters and make the model complexity independent of the WSI's size [35–37].

2.2. Standardization

WSI's quality is determined by the quality of the entire slide preparation process which depends on the manual process of fixating tissue, cutting slices using a microtome and staining of the histological slides. In addition, the scanning can be done with different types of scanners and settings. All those steps may cause variations in WSIs and hinder automatic processing. WSIs can many times include artefacts such as blurring, tissue folds, air blobs and shadows, which degrade the quality of the image and reduce the performance of systems which analyse them. In addition, for some cancer types the tumors are removed by cauterization, leaving parts of the tissue damaged and without diagnostic information.

Chromatic variability of WSI images can be significant between labs, i.e. inter-hospital, due to stain, protocol and acquisition system differences. Also the intra-hospital variability can be large due to lack of uniformity of the stains used, difference in thickness of tissue slides, age of the slides prior to scanning, etc. Dealing with colour variation is imperative to facilitate an analogous outcome in deep learning models. If it is not possible to provide a large and diverse enough training set that all possible normal variations are covered, different approaches can be followed to deal with slightly different colours of the WSIs: 1) colour deconvolution and normalization and 2) colour augmentation. Normalization methods can be divided into histogram matching, colour transfer, and spectral matching [38]. Colour deconvolution is usually considered as a branch of colour normalization aims at separating the stains in a WSI [24,39]. Colour augmentation focuses on simulating realistic stain colour variations of the training data [40]. Colour normalization has to be done both during the training of models and during prediction while colour augmentation only in the training stage.

Fig. 3 and 4 shows some examples of the heterogeneity existing in WSIs as for the presence of artefacts and colour variability. Data heterogeneity joined with the common use of proprietary file formats in the digital pathology field makes image standardization of paramount. Although the DICOM standard, widely used in radiology, now provides support for Whole Slide Imaging (http://dicom.nema.org/Dicom/DICOMWSI/) and the first standard-based commercial products are emerging on the market, interoperability in digital pathology is still more vision than reality.

2.3. To label or not to label?

Artificial intelligence algorithms are data-based and data-hungry, i.e. a lot of data is needed to be able to make good AI models. AI models can be learned by supervised, semi-supervised and unsupervised methods. The simplest and most straightforward strategy is supervised learning, where training data has truth labels used in back-propagation algorithms to tune the parameters of the model. In order to ensure clinically relevant labels, expert pathologists are needed to annotate/label the WSIs. Even semi-supervised or unsupervised methods will usually need a validation/test set that is labelled according to the task, to be able to test the performance of prediction models.

Due to its high clinical and scientific relevance, several Grand Challenges or competitions on computational pathology have been launched in the recent years with the aim of evaluating the performance of AI algorithms for the automated detection and classification of cancer and/or some relevant structures. The most important advantage of these events is to make WSI annotated datasets publicly available and allow fair and objective comparisons between different methods [41–50]. Other histological image databases can also be found on public data platforms such as Kaggle, Cancer Imaging Archive or National Cancer Institute, among others [51–53]. Despite the increase in the number of open-source histological image datasets, the lack of detailed, pixel-based, labels is still a problem in many cancer types.

Then, we will briefly talk through some possible learning strategies seen in computational pathology literature. A descriptive overview of the different deep learning schemes used in computational pathology is illustrated in Fig. 5.

2.3.1. Fully-supervised learning

Many of the publications in computational pathology is targeting fully supervised learning, where a training set is labelled consistently with the relevant labels for the task. Deep neural networks (DNN) based on fully supervised learning have very many parameters to learn and hence, require a large training set to produce good models and avoid overfitting.

Regarding fully supervised learning, there are two main approaches: 1) detect, locate or segment relevant objects in the image (such as mitosis, nuclei, cells, glands, tumor) [54–59] as a prerequisite for malignancy cancer assessment; and 2) direct image-level predictions (such as disease diagnosis, prognosis or grading) [60,61,36,37,62].

Note that detailed annotations, i.e. pixel-based labelling, of WSIs is a very time-consuming and complicated task because of the large size of the images and the fact that often only parts of the slides contains diagnostically relevant information. The annotation process is highly subjected to inter and intra-expert variability and there currently exists no defined protocol for the annotation of WSI for different tasks and diseases.

2.3.2. Weakly-supervised learning

Weakly supervised learning refers to learning a prediction model when the associated truth labels of the training set are in some ways less accurate than what the actual task requires. This occurs when we have training-sets that are labelled, but the labels are not exactly what we need for the final task, often referred to as *weak labels*. For example, a WSI has the label *cancer - high grade*, but we want to *localize* the region. Or a label says that this patient get recurrence of the cancer 6 months after the image was produced, but we do not know if there is anything in that image that actually is correlated with recurrence or not. In Section 1 the term image-based labels were introduced as opposed to pixel-based labels. In computational pathology an image-based label for a WSI will always be considered as a weak label, since the gigapixel images always will have (large) regions of the image that are not very relevant for the task.

Weak labels is also a "weakly defined word" in that it covers different situations, like where all of the training data is somewhat labelled, but not very precise, or that some of the data have missing labels. It can for example mean that the WSI only contains some metadata information like diagnosis or follow-up, but no details in which region of the image that was diagnostically important [63]. Another example of weak labels in WSI is if some areas in an image is marked as belonging to a type of tissue, or a cancerous region, whereas it might be other regions in the same image that are not labelled. A third example is if regions are just roughly outlined.

One strategy in weakly labelled data is to combine clustering ideas by measuring proximity in content as well as classification ideas measuring proximity in output labels and features at different layers [64] [65]. Another popular and successful strategy includes Multiple Instance Learning (MIL), where multiple instances are put in a bag. The bag is considered positive (to have a specific

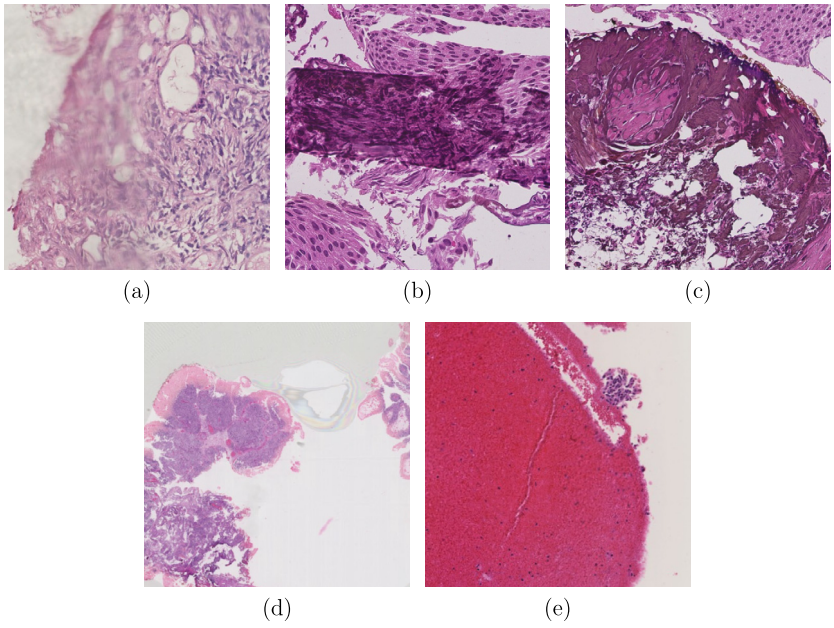

Fig. 3. Presence of artefacts in WSIs: (a) blurring, (b) fold, (c) burned/cauterized tissue, (d) air bubble, (e) blood.

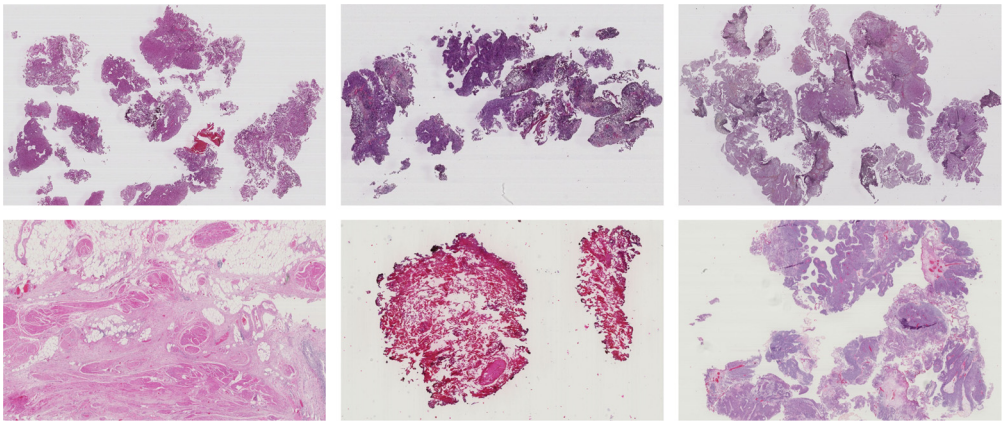

Fig. 4. Chromatic variability in WSI in bladder tissue samples. First row: Images acquired with a Leica SCN400 scanner by Stavanger University Hospital. Second row: Images acquired with a Hamamatsu NanoZoomer 2.0HT scanner by Erasmus Medical Centre Rotterdam. Even when the slides are scanned using the same hardware and at the same hospital, there is noticeable colour variation in the images.

label) if at least one instance in the bag is positive [66] [67]. Other strategies includes attention-based learning [35]. Other examples of publications based on weakly supervised learning of WSI can be found in [68,69].

2.3.3. Semi-supervised learning

Semi-supervised learning usually refers to situations where parts of the training data is fully and consistently labelled, and other parts of the data is not labelled at all. A very relevant question is how properties of the data can be used to improve decision boundaries and to allow for classification that is more accurate than that based on classifiers constructed using the labelled data alone [70]. Some semi-supervised approaches make additional assumptions that link the input features to the decision function, for example like cluster assumption, i.e. close in feature space should mean the same class label [66]. Another way to utilize such semi-labelled data-sets is by using *autoencoders*, where the unlabelled part of the data can be used to learn a feature extractor. This can later be connected to a classifier, and the labelled part of the data can be used to learn the classifier and potentially fine-tune the feature extractor. Examples of autoencoders used in computational pathology can be found in [71,72]. Other strategies in insufficient labelled data is to use models trained on small labelled training set to give initial labels to a larger set and boost the learning by adding only the labels the classifier is most confident of at each step and refine iterative in a self-learning scheme [73].

2.3.4. Unsupervised learning

The goal of the unsupervised learning is to learn patterns from unlabelled (or little labelled) data which made them desirable for the digital pathology community. Unsupervised methods includes techniques like clustering, autoencoders and generative adversarial networks (GAN), and there are examples seen in computational pathology [74–77] and we will probably see more unsupervised methods in years to come since unsupervised learning is an active field of research. Most unsupervised approaches aim to maximize the probability distribution of the data, subject to some constraints, to group data according to the target task. Current approaches usually require normal/healthy samples, that should be easier to obtain for training, in order to detect any deviations from such normal data without the need for labelled data. However, the overall performance still lags significantly behind supervised approaches [78]. *Unsupervised transfer learning* solutions such as unsupervised domain adaptation (UDA) or few-shot learning (FSL)

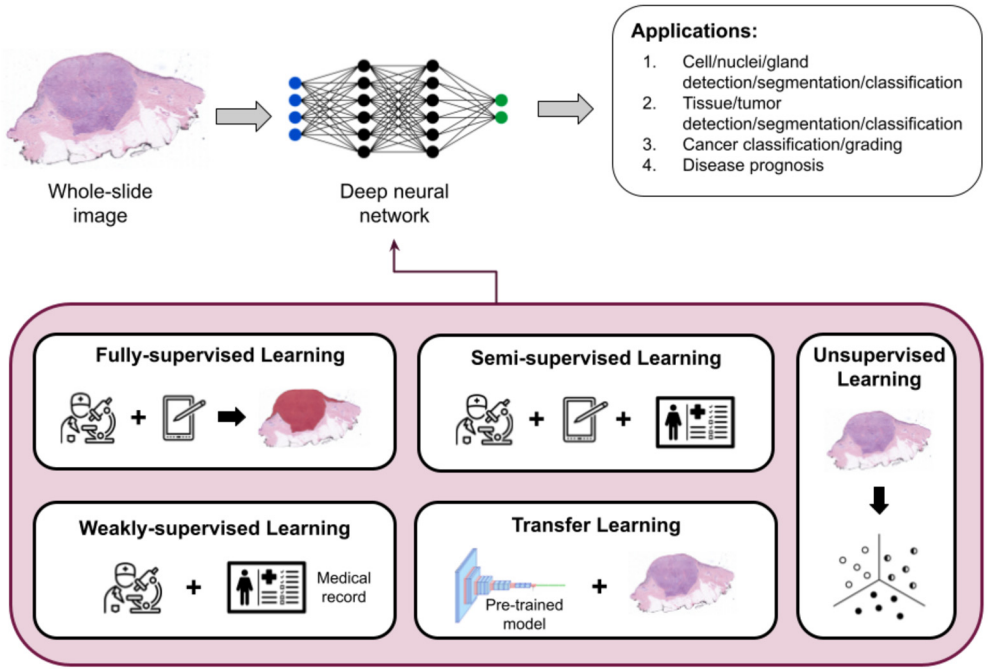

Fig. 5. An overview of deep learning schemes in computational pathology.

[79,80] are also attaining increasing attention in the computational pathology field. Another promising subclass of unsupervised learning is *self-supervised* learning in which convolutional neural networks are explicitly trained with automatically generated labels [81–83].

2.3.5. Transfer learning

Transfer learning refers to when a model trained for a task or type of input-data is used for a new task or other types of input-data. The model can be used without any further learning. More commonly, the feature extractor part of the model is used as a backbone for a system. A new classifier part is added to the feature extractor part, and a small labelled training-set is used to learn the classifier in a supervised learning setup. Depending on the size of the training-set, the transferred model can be frozen (unchanged weights) or fine-tuned using the small labelled training-set.

Among the different deep learning schemes in computational pathology, transfer learning is the most popular and widely adopted, usually using ImageNet pre-trained models such as Inception, ResNet, VGGNet, etc. to transfer the features learned on such source task to weakly related or unrelated target tasks as cancer classification/grading or disease prognosis [84–88,30,89]. Domain adaptation is a particular case of transfer learning that utilizes labelled data in relevant source domains to execute new tasks in a target domain and this has been applied to computational pathology [90,91]. Stain transfer and normalization methods can also be considered as a transfer-learning problem [92,72]. Transfer learning is much used in medical applications in general and its popularity lies in overcoming the massive problem of getting enough labelled data. It is a new direction with great potentials.

2.3.6. Other ways to label

Since the use of pathologists to label WSI in very large quantities is time-consuming, very laborious, and quite costly, another trend in the computational pathology field is to combine different methods to annotate large sets of WSIs: i) classic annotation by highly experienced pathologists, ii) multiple annotation by less experienced pathologist following *crowdsourcing* methods [93,94], and iii) a combination of human pathologist and automatic annotation through *active learning* [95,96]. The combination of different labelling approaches is illustrated in Fig. 6. This will not restrict the annotation to expert pathologists but will allow to facilitate the image annotation process involving pathologists with different grade of expertise or even researchers with medical knowledge (non-pathologists) that can conduct labelling under a strict statistical quality control. First, crowdsource tagging can be progressively added to the pretrained models to verify whether the labelling quality levels are maintained in terms of predictive performance when compared to models trained exclusively with labels provided by board certified pathologists. Secondly, integrating Active Learning into the annotation protocol will accelerate the annotation by introducing iterative annotation (use all available annotations - train intermediary model based on all currently available annotations - use the manually curated output of intermediary model to augment intermediary annotations - repeat).

3. Other future directions

3.1. Open up the black box

Deep image classification and prediction models can appear as a black box, where data is sent in, and a class or prediction is outputted without a good way to see why that particular prediction was made, or to, for example, *localize* the area in an input image that contributed most to the decision. If the training data used to learn deep neural networks is biased, the models will learn and adopt these biases. In addition, systems can be misled by perturbations in the input [97]. Especially in medical applications, the black box models can be seen as negative, since a high degree of trust is needed in decision-making. However, recent developments have allowed data scientists to gain insights in relation to "what the algorithms see", moving "from black box to glass box" [98].

Explainable AI, sometimes abbreviated as xAI, and explainable neural networks comprise a relatively new research field within the machine learning community, which is increasingly looking into ways to trace back the decisions through the layers of the network, making decisions somewhat transparent [99,100]. In the European General Data Protection Right (GDPR) laws, there is a

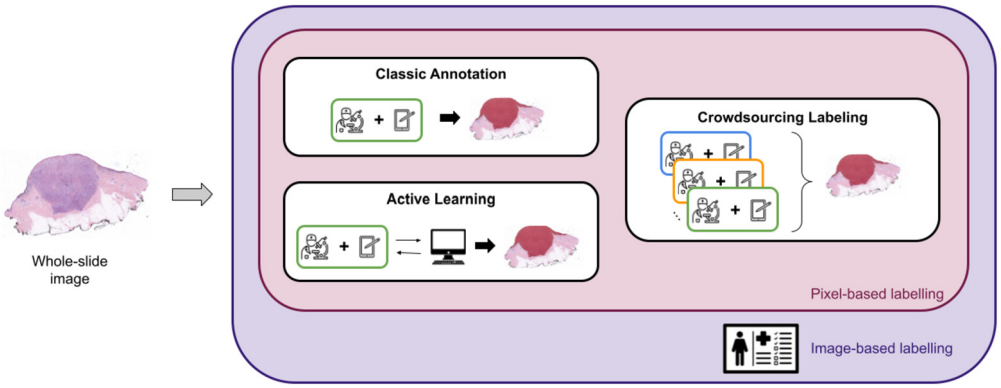

Fig. 6. Labelling approaches in computational pathology.

"right to explanation" embedded, emphasizing the need for interpretability in algorithms. Nevertheless, transparency might come at the cost of accuracy; thus, the right level of transparency should be sought. Interpretability may be understood as providing visual or textual presentation of how the model makes the connections between input features and output predictions [101]. Algorithms may be built as inherently interpretable or, as a way to not affect the accuracy of the model, following a highly accurate model and later using re-representation techniques to provide an explanation of the behaviour of the algorithm [101].

xAI tries to answer questions like i)"How does a learned feature affect the prediction?" and ii) "Which learned features contribute to a selected prediction?", which can increase the trust level of deep neural network based algorithms for medical applications. For questions ii) Break-down (BD) plots and shapley Additive Explanations (SHAP) [102] are examples of methods suitable with a limited number of features, whereas Local Interpretable Model-agnostic Explanations (LIME) [103] is an example of an algorithm that is more suited for image analysis and can be used to explore question i). We believe that an important future direction of computational pathology is to explore and adapt such algorithms to increase the interpretability of the developed neural networks to ensure the clinical reliability and the acceptance by pathology community. Attention-based models are also an alternative to increase model interpretability. Although attention units are not trained with the aim of creating human-readable explanations, they do directly reveal a map of which information passes through the network, which can serve as a form of explanation [104]. In addition, xAI opens a way of discovering new image patterns that pathologists may ignore but can be relevant in similar cases with different clinical progression and that are currently an unsolved problem in the medical community. The topic of xAI is already getting some attention in computational pathology [105,106].

3.2. Data fusion

Clinical and histopathological features alone are currently unable to predict the clinical behaviour for all carcinomas and the combination of data has become increasingly important for personalised diagnosis and prognosis. AI algorithms can combine the features extracted from digital histological images (WSIs) with proteomics through immunohistochemistry (IHC) data, epigenetic and genetic information, spectroscopic images and even with other imaging techniques. The comprehension of the molecular mechanisms which allow for the cancer dissemination can be an essential step in the prediction and prevention of the metastasis process. Incorporating proteomic data from IHC analyses adds a layer of significant data to the analysis process. Epigenetics has emerged as a frontier science of biology which has an important role in the progression and diagnosis of some tumours. Spectroscopy is a highly promising optical technology in the combined identification and localization of pathophysiological cell and tissue alterations.

Different powerful, in-vivo, noninvasive techniques such as magnetic resonance imaging (MRI), optical coherence tomography (OCT), endoscopy or ultrasound imaging are also widely used for the early detection of cancer and can be invaluable in the evaluation of the progression of a tumor. Although this kind of analysis is usually done before the biopsy and therefore prior to the histopathological examination, its results can be significant in providing pathologists with annotations of regions and features of interest. Therefore, the fusion of WSIs with other data sources may deem relevant in the future of computational pathology and can help professionals in detection, diagnosis, prognosis, treatment and monitoring of cancer lesions.

The fusion of multiple data sources can be performed following both early and late fusion strategies. In the late-fusion modality, classification algorithms for diagnosis and prognosis are developed for each of the data types separately, and fused at a later stage. In early-fusion strategies, the system incorporates all the different types of data input from the start, and learns to make predictions as a single output which processes all the different datasets.

3.3. Secure and efficient role-based data sharing

One of the key factors to boost research and technical development in a particular area is that researchers get access to relevant data. This is a major drawback for many medical applications, since the privacy regulations around medical data often only allows the data to be used for a particular research project and under strict regulations. Full anonymization of data is sometimes hard to do for different reasons, one can be that it is desirable to connect followup information in the future with a particular data-point. The computer science society is currently giving a lot of research effort to find secure solutions for role-based sharing of data and metadata, using smartcontracts and blockchain technology [107,108]. With secure ways of sharing data so that *you are authenticated and you only get access to the part of the data you are authorized to see*, it is possible with easy sharing for second/experts opinion, for running samples on other automated diagnostic systems, and sharing to the research community for developing new models and methods or adapting existing models. We believe that computational pathology will benefit from the possibilities given by secure and efficient role-based data sharing, and that this should be an area for future development.

4. Conclusion

Pathology has repeatedly been highlighted as being ripe for innovation in terms of workflow efficiency and more accurate diagnostics. Despite a boost in sales of digital pathology systems,

diagnostic pathology in practice today is still a slow and cumbersome process that relies heavily on the subjective interpretation of a microscopic image by a qualified pathologist. AI addresses the challenge to modernize and improve pathology departments' workflow optimising current diagnosis, prognosis and monitoring processes to help pathologists to reach better-informed decisions. Computational pathology can provide repeatable and automatic diagnostics as a second opinion, predict prognostic values and provide the pathologists with region of interests. It has potentially the power of reducing the workload on the pathologists and reduce the turnaround time at pathology labs, and is becoming an area of research and rapid development.

Within this context, in this paper, we have analysed the present, some of the challenges and some future directions of computational pathology. The possibly largest challenge for all medical AI applications is the lack of labelled data. The research community is working from different angles to come with solutions to this problem in all applications. In computational pathology, it is a specially large problem due to the nature of the images and high data heterogeneity due to colour variability and tissue/disease-related variations. Image processing algorithms are usually used for WSI preprocessing (e.g. for colour standardization) with the aim of alleviating the problem of data diversity and scarcity. Although transfer learning is the most popular deep learning scheme used in computational pathology since it overcomes the problem of getting enough labelled data, new directions have arisen such as weakly-supervised, semi-supervised or unsupervised learning via multiple-instance learning, attention-based models, autoencoders, generative adversarial networks, few-shot learning, domain adaptation or self-learning schemes, among others. These approaches are gaining popularity and open up a whole new world of possibilities. In particular, we consider that the combination of weak label strategies with active learning and crowdsourcing scenarios will be a very promising line of research and widely addressed in the close future. It would remove some of the workload from clinical experts and manual annotation obtaining clinically satisfactory performance with minimal annotation effort.

In addition, we believe we will see an increased focus on explainable AI for computational pathology, which has the potential of both gaining the trust of pathologists to use AI, but also provide us with *new knowledge*, not solely mimicking pathologists to reduce workload. Fusion of different data sources can also provide new insights, and we believe we will see more of that in computational pathology in years to come. In parallel, we believe that computational pathology will benefit from the possibilities given by secure and efficient role-based data sharing which would be useful for making more data available across research consortium and countries and overcoming the massive problem of lack of data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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