The American Journal of Pathology, Vol. ■, No. ■, ■ 2021

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The American Journal of PATHOLOGY

ajp.amjpathol.org

MINI-REVIEW

Generative Deep Learning in Digital Pathology Workflows

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Accepted for publication February 24, 2021.

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Many modern histopathology laboratories are in the process of digitizing their workflows. Digitization of tissue images has made it feasible to research the augmentation or automation of clinical reporting and diagnosis. The application of modern computer vision techniques, based on deep learning, promises systems that can identify pathologies in slide images with a high degree of accuracy. Generative modeling is an approach to machine learning and deep learning that can be used to transform and generate data. It can be applied to a broad range of tasks within digital pathology, including the removal of color and intensity artifacts, the adaption of images in one domain into those of another, and the generation of synthetic digital tissue samples. This review provides an introduction to the topic, considers these applications, and discusses future directions for generative models within histopathology. *(Am J Pathol 2021, ■: 1–7; https://doi.org/10.1016/j.ajpath.2021.02.024)*

Clinical histopathology is at an exciting paradigm shift, with many laboratories replacing traditional microscopy with high-resolution scanners and large digital displays. Unlike traditional slides, digital images can be shared electronically, marked up simultaneously by multiple pathologists, and assessed automatically.[1] The deployment into clinical practice of systems that automate and augment diagnostic reporting is expected to lead to a significant increase in assessment capacity alongside quicker reporting times. This article provides a brief introduction to deep generative models, reviews their current use in digital pathology, and envisions their future applications within the field. To contextualize this work, deep generative models are discussed in relation to the current state-of-the-art deep learning techniques for pathology and the problems that generative techniques can solve within a conventional pipeline.

Before discussing the place that generative models could take in the field of automated histopathology, it is necessary to describe the current typical workflow of machine learning in digital pathology and some of the common issues that can hinder downstream reporting tasks. A taxonomy of data science tasks, independent of pathology, organized into five categories, undertaken sequentially: obtain, scrub, explore, model, and interpret (dataists, *http://www.dataists.com/2010/09/a-taxonomy-of-data-science*, last accessed September 18, 2020, are shown in Figure 1. This model can be used to understand the process of applying machine learning in digital pathology. Data are obtained through the fixing, staining, and scanning of tissue to transform into a set of whole slide images. These images are then scrubbed, or preprocessed, to remove artifacts and prepared to be used in the modeling phase. Tasks such as stain normalization, data augmentation, and patch generation fall into this category. In the exploration phase, resulting scrubbed data are analyzed, either automatically or by a human, to determine

Artificial Intelligence and Deep Learning in Pathology Theme Issue

Supported by the Sir James Mackenzie Institute for Early Diagnosis, University of St. Andrews, United Kingdom (DM) and Industrial Centre for Artificial Intelligence Research in Digital Diagnostics, United Kingdom, grant TS/S013121/1 (D.M., D.H.-B., P.D.C.).

Disclosures: None declared.

This article is part of a mini-review series on the applications of artificial intelligence and deep learning in advancing research and diagnosis in pathology.

https://doi.org/10.1016/j.ajpath.2021.02.024

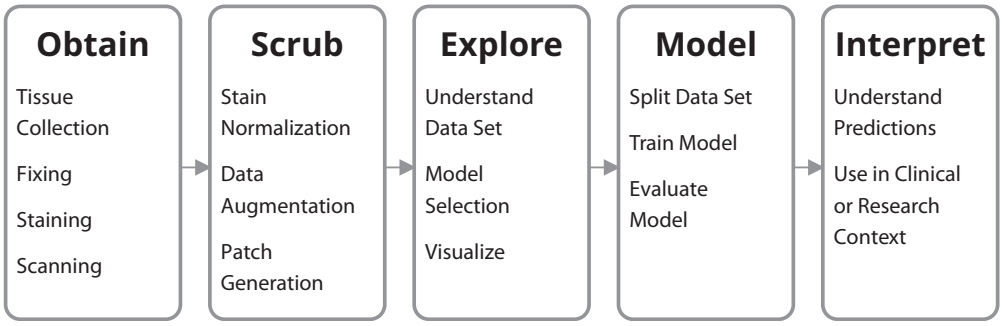

Figure 1 A taxonomy of data science tasks applied to automated whole slide image analysis.

an appropriate modeling technique, such as a specific neural network architecture. A large number of different pathologies and tissue types may be of interest in digital pathology. This makes it impractical to iteratively try every possible modeling technique, and in the case of ensemble learning, every combination of technique. The machine learning system is trained and evaluated during the modeling phase. In the interpretation phase, human pathologists are presented with the predictions of the model which can be used for clinical or research work.

The automation of whole slide image (WSI) analysis and diagnosis presents several significant challenges.[2] Foremost is the issue of data size; whole slide images are multi-gigabyte images in the range of approximately 100,000 × 100,000 pixels. This makes a direct application of modern computer vision algorithms on non-specialist computing hardware impractical. Typical solutions to overcome this include: downsampling the image and breaking the image up into smaller subimages called patches.

Second, data availability is problematic for most researchers. Supervised machine learning requires labels for each sample. In WSI analysis, this may mean assigning a category to each slide as a whole, identifying a set of points of interest on the tissue, or drawing around areas to segment tissue types or pathologies. For each of these, a trained specialist in histopathology is required. The process is time-consuming and expensive, and there is often a lot of inter-observer and intraobserver variability between the labels provided by pathologists. As a result, data sets used to train automated digital pathology models tend to be small compared with those available in other computer vision subfields, such as ImageNet,[3] where non-specialists can straightforwardly provide labels (eg, labeling a cat versus a dog). This situation, however, has been improved by the release of tissue annotated open data sets, such as Camelyon16[4] and Camelyon17[5]. Furthermore, initiatives such as iCAIRD (iCAIRD, *https://icaird.com*, last accessed September 18, 2020) and Pathlake (PathLAKE, *https://www.pathlake.org*, last accessed September 18, 2020) provide large, well-annotated, and curated WSI data sets linked to clinicopathologic data. These make rich digital pathology training material widely available, albeit within narrowly defined clinical reporting and specific tissue types.

Third, WSI analysis experiences several domain-specific image artifacts caused by the process of surgical removal, fixing, cutting, staining, and scanning the tissue. These can include folds in the tissue, retraction artifact, variations in the application of chemicals in the staining process, small cracks and imperfections in the glass slide and coverslip, partial blurring of the image caused by focusing errors, and image resolution and compression differences between different scanners and file formats.

Despite these challenges, computer vision techniques based on supervised and weakly supervised learning have been used to successfully automate some common assessment tasks in histopathology. These include, for example, cell nucleus identification, pathology classification, and cancer segmentation.[6] Unsurprisingly, state-of-the-art results on slide classification tasks, such as the work by Campanella et al[7] on prostate cancer, basal cell carcinoma, and breast cancer nodal metastases, rely on large data sets.

Deep Generative Models

This section briefly introduces required terminology from computer vision, deep learning, and generative modeling before describing their uses in a digital pathology workflow. First, an image filter or kernel is a rectangular matrix that can be applied to parts of a digital image to extract information, called features, from it. To apply a filter, a dot-product is performed (component-wise multiplication followed by a sum) between the filter and a section of the image with the same dimensions. In computer vision, this operation is referred to as a convolution. By sliding the filter across the image and performing the convolution at each point, this operation can produce a new matrix, known as a feature map. Filters that recognize primitive features, such as horizontal or vertical lines, can be hand crafted; however, more complex features must be learned by the model. Neural networks are the most commonly used machine learning approaches.[8] A convolutional neural network[9] is a machine learning approach that enables image filters to be learned from data rather than programmed explicitly.

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Generative models are an approach to machine learning in which systems attempt to estimate the probability of a specific sample being picked at random based on training data.[10] Once there is an estimate for the probability density function over the training set, the model can be used to generate new examples. For example, a model can be trained to generate new images of cats by training it on a large number of images of cats. Generative models are contrasted with discriminative models, which estimate the probability of an output value given an input value (this includes classification and regression problems). Recently, generative models based on deep learning have shown promise in generating novel data across a range of domains and tasks.

The most effective techniques, such as generative adversarial networks (GANs)[10] and variational autoencoders,[11] come from a class of models known as latent variable generative models. In such systems, a model is trained that takes the lower-dimensional representation of data, called the latent space vector, and generates high-dimensional data from it. GANs and variational autoencoders differ in the way they are trained, but both conceptualize generation as decoding. By changing what data are passed in, as the latent space vector, model parameters can be learned that enable the model to perform data translation tasks. Figure 2 shows an example of a latent space vector and generated images. In their recent review of GANs in pathology, Tschuchnig et al[12] split the GANs up based on what kind of translation task the model is training for. This put the emphasis on task (eg, image-to-image translation verses label-to-image translation). The rest of this review describes how different generative models have been trained to perform different translation tasks and how these could be usefully applied to the automated reporting of a clinical task within a digital pathology pipeline.

Generative adversarial networks[10] are a class of generative model in which a network, known as the generator, is trained by having it attempt to trick a second model, known as the discriminator. The discriminator and the generator are trained simultaneously. During training, the generator is sampled from by having to translate noise into fake data. The discriminator is then trained on a combination of the fake data, labeled as fake, and the real data, labeled as real. The generator is then trained by having it generate fake data and asking the discriminator to predict labels for it. The training loss for the generator is based on how well the discriminator can tell them apart [ie, how well the generator can fool it (generating fake data that the discriminator classes as real)]. This simultaneous training procedure can cause GANs to both be computationally expensive and experience difficulty in converging to an accurate solution.

Generative Models in the Digital Pathology Pipeline

Generative models have the potential to overcome several issues that come up when developing computer vision systems for digital diagnosis and reporting. For example, data sets stained at different institutions can often have a lot of variation in color and intensity. It can be expensive and time-consuming to acquire high-quality labeled training data. Generative models can generate synthetic data sets to overcome this. They can also be used to virtually stain tissue, reducing the tissue preparation overhead.

Color and Intensity Normalization

During tissue preparation, particularly staining, variations in color and intensity can be introduced between different whole slide images. These artifacts can complicate the interpretation of the slide by pathologists and computers. When this occurs, similar tissue features can present differently or different ones similarly. Such artifacts are introduced from several sources, such as differences

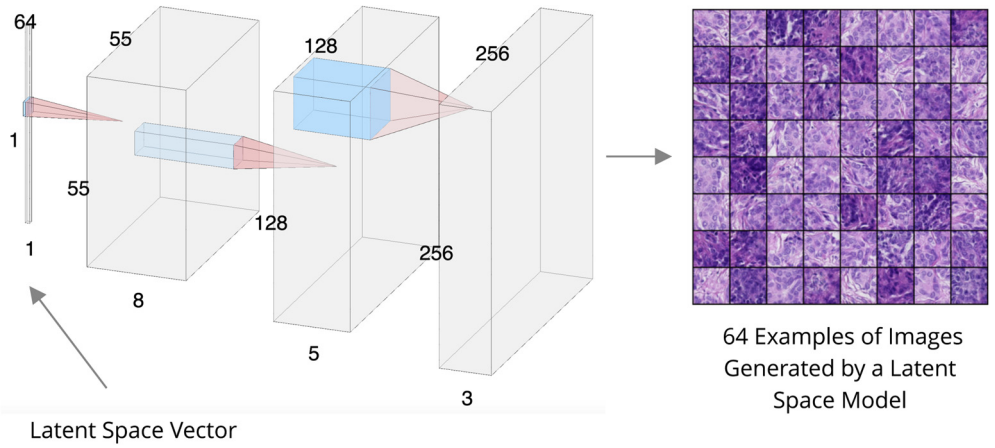

Figure 2 A low-dimensional vector is used to generate data in latent space models. In this example, a series of convolutions are used to achieve this transformation. The example output of the network shows 64 images, each 64 pixels wide and 64 pixels high.

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between scanners, the thickness of the cut tissue samples, and the amounts and concentrations of chemicals used in varying staining protocols. These issues can be mitigated in three ways: ignoring color information, training models to learn features insensitive to the artifacts,[13] or normalizing images to account for differences.

By converting the image to grayscale, much of the information provided by the staining process is lost. Analysis techniques for grayscale pathology images have to rely on other features (eg, texture and morphology),[14,15] leading to lower performance on downstream tasks. In other situations, artifacts can be compensated for by applying a large number of color perturbations to the training data so that a wide range of variations are presented to the model during training.[13] This technique requires the perturbations to be statistically similar to the color and intensity variations across the data to be assessed, information that is not always available, and requires increased computational and memory overheads because of the large amount of data augmentation.

Ruifrok and Johnston[16] proposed a novel method based on color-deconvolution that dependeds on user-determined color information to reconstruct images for each stain. This method provides state-of-the-art results for stain normalization but is limited in its applicability to extensive studies because the user needs to estimate the values used in the deconvolution manually. Magee et al[17] presented a method for estimating the required color deconvolution parameters from the image data, eliminating the need for user input. This work was extended by Khan et al[18] to account for image-specific color variations and to improve the training data used to separate the different stains.

A limitation of color-deconvolution techniques is their failure to take into account information outside of the image color (eg, tissue structure or texture). Generative models are able to address this limitation. Stain normalization can be thought of as an image generation problem. Generative models have proved useful for image generation and recently have been applied to generate normalized pathology slides. Three different approaches have been applied to this task: stain-style tranfer,[19] CycleGAN[20] based image-to-image translation, and Pix2Pix-based translation.[21]

Stain-Style Transfer

Neural style transfer[22] is an image translation technique that transfers the style of one source image onto the content of another to generate a target image. The terms style and content can be a little misleading at first; content refers to aspects of the image, like the shape and arrangement of nuclei and cells and the tissue architecture that they comprise; and style refers to aspects such as color, like the hematoxylin and eosin (H&E) shades, and texture (eg, the nuclear chromatin). Style representations are derived from correlations in between the same location in different activation maps of the same layer of a neural network. For example, there might be a filter that recognizes blue pixels and another that recognizes a curve. If they consistently activate together, then this would represent that curves are generally blue. Stain normalization can be thought of as a kind of style transfer from the source to the target; however, it is important that only the color distribution is transformed, not other histopathologic features.

Stain-style transfer[19] uses a modification on GANs to perform color normalization, as indicated by its application on patches extracted from the Camelyon16 data set.[4] The normalized patches improve tumor classification. In this technique, the input into the GAN generator is changed from noise to the unnormalized image. A conditional GAN[23] is then used in which both the generator and discriminator are trained to generate and discriminate class labels for each patch, in this case tumor or nontumor, in addition to the fake or real labels. On its own, this produces distortion in the patches' noncolor histopathologic features. To address these issues, two other loss functions were added to the system: reconstruction loss, to minimize the difference between the source and generated images; and feature-preserving loss, which derives a loss by comparing the activations of the final layer of the discriminator when the source and generated images are passed though the network. This approach improves the classification accuracy of a convolutional neural network−based model trained on image patches extracted from the Camelyon16 data set. BenTaieb and Hamarneh[24] propose a similar approach in which the generator architecture is replaced with a U-Net encoder-decoder style network, called the stain transfer network, and the discriminator is given an additional classification task. This approach was assessed on both classification and segmentation tasks, across three separate data sets, showing it can be used to improve the identification of a wide range of tissue and pathology types.

Pix2Pix-Base Image-to-Image Translation

Pix2Pix[21] is an extension of conditional GANs, which, like other image-to-image translation models, learns the mapping from one image domain to another. The difference with Pix2Pix is that it also learns a loss function to train the translation model. This means that models based on Pix2Pix can be trained to translate between different domains without the need to specify a specific loss function for that translation, something that is hard to do. Like conditional GANs for image-to-image translation, Pix2Pix requires image pairs, one from each domain, as example translations. Salehi and Chalechale[25] applied this approach successfully to the stain normalization using five different H&E data sets. The method involves destaining the patches by reducing them to grayscale, before synthetically restaining them in a way that ensures that the color is consistent. This is similar to the artificial staining proposed by Rana et al,[26] discussed under data adaptation, and has been shown to perform well across a range of statistical measurements comparing ground-truth stained images against those restained using the GAN. This indicates that they may improve downstream

assessment tasks, such as tumor classification and segmentation, in a similar way to the stain-style transfer techniques.[19,24]

CycleGAN-Based Image-to-Image Translation

One of the key disadvantages of Pix2Pix is the need for paired images from the source and target domain (eg, coregistered images before and after staining). CycleGAN[20] bypasses this requirement, allowing models to be trained to translate from a source to a target domain without the need for paired examples. This is done by training an inverse mapping from the source to target domain, at the same time as training the translation. By comparing the original image with one that has had the forward and inverse transformation applied to it, a loss called cycle-consistency loss is derived. When the generator is trained, cycle-consistency loss is minimized, as is the conventional adversarial loss derived from trying to fool the discriminator.

de Bel et al[27] showed that modifying the original CycleGAN[20] to use a U-Net[28] style architecture made it more suitable for use with pathology images. This system can be used to artificially stain images to a high quality. The technique was applied to two data sets of renal tissue sections stained with periodic acid-Schiff from different staining centers. Models trained using the normalized data had increased accuracy when segmenting various objects of interest within the renal slides, such as arteries, tubuli, and glomeruli. However, the system was able to generate changes in texture, something that breaks the constraint that the transform should preserve noncolor tissue features and potentially introduces unwanted bias into the generated data sets.

Data Adaptation

Data adaptation is the task of taking the data in one domain, such as H&E WSIs, and translating them into images that resemble those in a different domain, such as immunofluorescence WSIs. This can be useful as a data augmentation technique, allowing for images labeled in one domain to be used effectively for learning in another domain. Doing this relies on the image translation process retaining the correct labels. For example, if something is labeled as a cell nucleus, it has to still look like a cell nucleus once it has been translated.

One possible use of this data adaptation is to enrich patches with additional channels showing different fluorescence labels that highlight different kinds of information. This is called multiplexing and has traditionally been achieved though relabeling the same tissue multiple times and scanning in each fluorophore separately. There are two issues with this: after multiple relabeling, the tissue quality begins to degrade; and scanning requires the slides to be precisely aligned to allow the tissue to be coregistered. By doing virtual staining, the tissue is not degraded, and because a single scan is used, there are no issues related to alignment.

A histopathologic-to-immunofluorescence translation model that uses Pix2Pix[21] has been introduced by Burlingame et al.[29] They adapt Pix2Pix by adding an adaptive regularization term during training that changes based on the prevalence of stained tissue in the patch. Patches with a low amount of stained tissue are penalized. This composites for the relative ease of translating patches with low amounts of tissue. The system's ability to generate realistic immunofluorescence stains from H&E stains opens up the possibility of quickly providing information about cellular complexity when only a standard H&E stain is available.

Another possible application of image translation is artificial staining, in which the source domain is an unstained image and the target is stained ones. If it is possible to do this in a consistent way, it can remove the need for laboratory-based staining with its associated variations, requiring stain normalization, and for the potential of human error. Rana et al[26] apply a modified Pix2Pix[21] model in which the generator made use of a U-Net architecture[28] to translate between an unstained WSI taken from a prostrate core biopsy and virtual H&E stains of the same image. Examination of the virtually stained images by pathologists showed that the system correctly stained many different histologic structures, including glands, stroma, nerve, and vascular spaces.

Data adaptation can also be used as a form of data augmentation. In DASGAN, Kapil et al[30] use a CycleGAN[20] to generate virtual programmed death ligand 1 stains from existing cytokeratin stain that has been marked up with a costly segmentation label. These data were then used to train an image segmentation model for the tumor epithelium that outperformed the same model without the additional data.

Data Synthesis

Data synthesis is perhaps the most exciting prospect for generative models, especially in the field of artificial intelligence–based reporting of histopathology. In digital pathology, generating a ground truth is expensive and time-consuming. If accurately labeled synthetic samples could be generated, then this problem would be alleviated. The amount of data would only be limited by the resources available to run the generative model. However, a conundrum exists here, and data synthesis is challenging. If there is enough data to train a generative model to generate new labeled data, then it is likely there is enough data to train an accurate classifier. Useful data synthesis requires one or both of two things: that the generative model is able to learn different representations, more useful in generation, than a possible classifier, or that extra information is somehow added to the generative process (eg, using a guide image).

PathologyGAN[31] is a study that undertakes the first of these approaches. It uses BigGAN,[32] a version of GANs that

applies orthogonal regularization to the generator, allowing for more control over the generator's output. PathologyGAN uses a relativistic average discriminator,[33] a modification to the discriminator that estimates the probability that a real sample is more realistic than a randomly sampled fake data point. This addition was shown to improve the quality of the generated images and converge faster. This system enables the generation of large data sets suitable for training.

The generation of new images can also be achieved by reformulating the problem as image translation, as shown by Wei et al.[34] They take normal colonic mucosa images and generate synthetic colorectal polyp images on them. As with many other image-to-image translation models, their system is a variation on CycleGAN.[20] They train the system on a data set that is filtered to only include patches that can be unambiguously classified using a ResNet[35] classifier. Using this approach enabled them to augment their existing colorectal histology a classifier with a 10% improvement in area under the curve. The field of data synthesis is still wide open for follow-on work, as noted in both of these articles.

Future Directions

High-quality synthetic data sets with labels generated using GANs[31,36] improve the performance of discriminative models trained on their data. Currently, these techniques are applied to the synthesis of patches, rather than complete whole slide images. When diagnosing, a human pathologist mostly works at a low magnification (eg, $\times$10) and relies on architectural features that are lost when the image is broken down into patches. There is potential to train on similar low-magnification images to exploit these features. A single WSI can be split into many thousands of patches, meaning that the training sets for patch classifiers are many times larger when the image is patched at high magnifications. At a lower magnification, the number of images available for training reduces dramatically, making such approaches less feasible. This is where generative approaches, such as those above, could be used to generate a large number of low-magnification synthetic images, containing architectural features. Using other kinds of image synthesis, such as traditional computer graphics techniques, in combination with generative models[37] may provide a useful method in this domain and is an exciting future direction.

Generative models have the potential to enable medical data of all kinds, including pathology slides, to be used to train machine learning models without them needing access to the original patient-identifiable data set. Training a model on nonanonymized data and then using the model to generate a new artificial anonymous data set may provide a way to overcome the clinical firewalls that, because of patient confidentiality, prohibit many researchers accessing the original data. This topic is the subject a large amount of research within the deep learning community.[38–40] Sufficiently deep generative models are capable of memorizing their training data in a way that can cause potentially confidential information to leak into any synthetic data. This has important implications for data governance going forward. To make generative models public, it is critical to ensure they are trained in such a way that removes the possibility of confidential data being leaked into any synthetic data set, and therefore, guidelines for doing this while maintaining privacy are required and will need to be adhered to.

Conclusion

This article reviews recent advances in the application of generative models to digital pathology. Work in this domain seeks to address issues of color and intensity artifacts, data adaptation, and data synthesis, and how generative models can address these. Generative models can assist with several open challenges in the digital pathology workflow. Multiresolution WSI synthesis may provide a way to train deep models that exploit architectural tissue features in a way that is currently unpractical because of a lack of data. Additionally, differential privacy for WSI data sets may allow for a much larger amount of useful data to be released publicly. The application of generative models has proved useful in improving digital pathology workflows, and this fast-developing technology holds much promise in this field.

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