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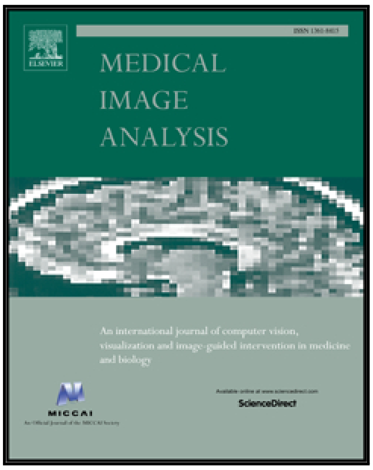

Special Issue on Computational Pathology: An Overview

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Special Issue on Computational Pathology: An Overview

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The field of Digital Pathology has grown considerably in the past few years. The early years focused primarily on the scanning and remote viewing of histopathological images. However, as the use of tele-pathology has become widespread, the emphasis on digital pathology has increasingly moved towards the application of image analysis and artificial intelligence techniques to maximize the meaningful information that can be extracted from tissue sample with the final aim of aiding the diagnosis of the pathologist. Interestingly, with advancements in computational algorithms for digital pathology, the types of problems that researchers have embarked on have evolved from focusing solely on decision support for the pathologist to also to begin to prognosticate disease outcome, predict tumor biology and also therapeutic response.

This special issue of *Medical Image Analysis* is a collection of 15 original and peer-reviewed articles that focus on the growing field of Computational Pathology. The call for papers of the special issue was launched on the 31st of July 2019 with a deadline of the 31st December of the same year, with Drs Anant Madabhushi and Constantino Carlos Reyes-Aldasoro serving as Guest editors for the special issue. In total 38 manuscripts were received. These manuscripts underwent the regular MedIA peer-review process with an average of 3 reviewers per manuscript. Fifteen manuscripts met both the high standard for acceptance of the journal and deadline for publication and these were accepted into the special issue. Twenty-one manuscripts were rejected and two were transferred to a different journal. The average review and processing time, from the day papers were submitted until final acceptance was approximately 45 weeks.

Broadly speaking, the papers fell into four different categories. Firstly, and expectedly, there were a number of papers focused on new approaches for deep learning being applied to computational pathology. A second group of papers focused on novel hand-crafted and feature engineered based histomorphologic features for disease characterization and prognosis prediction. A third cluster focused on novel computational approaches to help alleviate the burden associated with manual annotation of pathology images for training of machine learning algorithms. Finally, a fourth cluster included a review of state-of-the-art approaches in computational pathology and another focused on documenting a recently concluded computational pathology challenge.

In the first cluster of paper, two articles focused on multi-scale and multi-resolution deep learning networks. The use of multiple resolutions is modeled on the way human pathologists tend to assess the slides, typically zooming in and out across various magnification to appreciate global tissue, cellular structures or nuclear details. **Schmitz** *et al.*(Schmitz et al., 2021), present an evaluation of multi-scale fully convolutional neural networks, which are compared against a baseline single resolution U-Net. The evaluation is performed in three publicly available data sets: (PAIP 2019: hepatocellular carcinoma segmentation; BACH 2020: breast cancer segmentation; CAMELYON 2016: metastasis detection in lymph nodes) and demonstrate that the use of multiple resolutions, where global context aids local contextual information, can outperform networks trained at single or individual resolutions. **van Rijthoven** *et al.* (van Rijthoven et al., 2021) describe a multi-resolution convolutional neural network called “HookNet”, where “hooking” refers to a mechanism of concatenation of feature maps in a downstream convolutional layer. HookNet combines context and details at multiple resolutions and evaluated in the context of semantic segmentation of breast cancer and lymphoid structures and germinal centers in lung cancer.

The importance of interpretable outputs and the utility of computational pathology in a clinical setting is touched on in two papers. **Thomas** *et al.*(Thomas et al., 2021), present a U-Net-based architecture that focus on the accurate segmentation of common skin cancers in order to classify them into meaningful dermatological classes. **Dov** *et al.*(Dov et al., 2021), also focus on providing accurate predictions of thyroid malignancies from cytopathological images to allow augmentation of human decisions. Their approach involves breaking down the concept of a “single or unique bag” from which patches are extracted, moving towards the idea of a bag-level malignancy prediction driven by a two-stage deep learning algorithm.

Three papers in the special issue also focused on the issue of robustness of the neural networks vis-a-vis image rotation. **Wang** *et al.* (Wang et al., 2021), present a hybrid neural network based on multi-task and ensemble learning to the problem of segmentation of hepatocellular carcinoma lesions. The network splits the processing into interrogating individual image patches, predictions at the patch level are then aggregated through an ensemble network. The network was tested on three publicly available data sets and provided state of the art results. **Lin** *et al.* (Lin et al., 2021), analyze the difficult problem of Chromosome karyotyping, i.e. the identification and analysis of individual chromosomes. The process is relatively simple when chromosomes are fairly straight and separable from each other, but most segmentation approaches are challenged by overlapping chromosomes and the chromosomes presenting in the form of uneven intensity bands. The authors present a weakly supervised ResNeXt approach that attempts to separate and segment touching and overlapping objects, the approach yielded accurate state of the art results. **Lafarge** *et al.* (Lafarge et al., 2021), describe the encoding of the geometric structure of the special Euclidean motion group SE(2) into a convolutional neural network, which is then evaluated in the context of mitosis detection, nuclei segmentation and tumor detection. The process creates various layers that include a maximum intensity projection over rotations, providing rotation-invariant properties. State-of-the-art performance was obtained without the need for data augmentation by image rotation.

A second cluster of papers in this special issue focused on new feature engineering or hand-crafted feature extraction approaches for problems relating to classification and prognosis prediction. **Xu** *et al.* (Xu et al., 2021) presented a new feature engineering approach for the problem of staging of spermatogenesis. Defects in the spermatozoa can lead to infertility. New histomorphological features based on derivative of Gaussians and textures were combined with a U-Net architecture to enable discrimination of the different stages of spermatogenesis. **Lu** *et al.* (Lu et al., 2021), presented a new approach (Flock) to characterize local spatial cellular heterogeneity in the context of lung and oropharyngeal cancers. Across several hundred patients across the two different cancer indications the authors were able to show that the Flock features were able to predict human papillomavirus (HPV) status in oropharyngeal cancers, additionally these features were also able to predict risk of disease recurrence in early-stage lung cancer.

A third class of papers showcased in this special issue focused on tools and methodologies for improving existing methods for segmentation and classification. Recognizing the overhead cost of training machine learning algorithms in computational pathology. **Pati** *et al.*(Pati et al., 2021), presented a new approach to reduce the effort of annotation through the use of a co-representation learning framework that exploits categorical cross-entropy as well as a neighborhood-aware similarity sampling. **Riasatian** *et al.* (Riasatian et al., 2021), described KimiaNet, an architecture based on a DenseNet but that has been trained with more than 240,000 patches from histopathology images. **Koohbanani** *et al.*(Alemi Koohbanani et al., 2020), described a tool to provide precise annotations of cells and nuclei with a CNN-based approach that only requires a single click inside each object. For large structures such as glands, instead of a click, a squiggle is required. The tool called NuClick was tested at different scales and across different applications such as blood smear images and immuno-stained lymphocytes. **Ciga** *et al.* (Ciga and Martel, 2021) described a tool to assist the annotation of histopathology images. As opposed to NuClick that focuses on individual cells or nuclei, the method presented by Ciga *et al.* works at the patch level.

Finally, there was a review paper by **Srinidhi** *et al.* (Srinidhi et al., 2021) offering a comprehensive review of deep learning technologies that have been applied specifically in the context of histopathology. The survey covered 130 papers published between 2013 and 2019 and complements other reviews on deep learning that are more general and not specific to digital pathology (e.g. by Litjens *et al.* (Litjens et al., 2017) and Meijering (Meijering, 2020)). Finally, **Kim** *et al.* (Kim et al., 2021) presented a paper on the results of a computational pathology challenge (PAIP), organized in conjunction with the Medical Image Computing and Computer Assisted Intervention (MICCAI) Conference in 2019. Challenges have become a useful vehicle to compare different algorithms on real world data sets. This challenge focused on liver cancer segmentation and viable tumor burden estimation. The challenge organizers provided 100 whole slide images divided into training, validation and testing sets. A total of 28 groups participated with 64 submissions. The top three algorithms were based on a UNet architecture, complemented with an EfficientNet-B4, SE-ResNeXt101 and DenseNet121 backbones.

In summary, the 15 papers selected for this special issue represent the latest advances in machine learning and computer vision approaches in the area of digital pathology. While at the time of writing, no computational pathology approaches are currently in the clinic, the advances described in this special issue suggest that clinical deployment of AI tools for pathology may be sooner rather than later.

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