Q1 Report: MIL in Pathology

Executive Summary

The primary purpose of this report is to review the implementation ability of multi-instance learning (MIL) in the field of pathology image analysis based on supervised machine learning methods. Several characters in pathology analysis are summarized, revealing the benefits of applying MIL facing the research need. A particular work is reviewed in this report to explain the general method of MIL in pathology as a detailed example. In future works, MIL can explore unidentified features and increase the interpretability beyond its analyzing strength in current studies.

Introduction

The pathology analysis has been used as the golden stander in diagnosing many cancers worldwide, with the observation work under the microscope by the pathologist [1]. As an automated attempt, the usage of a computer-aided diagnosis system aims to reduce the pathologist's workload in clinical practice. Based on the inspiring progress and advancement of machine learning in solving image classification tasks in the computer vision field, the machine learning method is widely applied to the analysis of digital pathology images [2]. In recent years, the new method enables the entire sample slide sampled in the surgery to be made to the digital sample (whole slide image, WSI) with a scanner. With the accumulated WSI datasets, many machine learning research based on the sample level pathological analysis can be viewed recently [2-5]. Several works explored the public datasets, including The Cancer Genome Atlas (TCGA) [6], etc., and the problem of insufficient labels exists the same way as the field of computer vision. In many WSIs, the exact location of the region of interest (ROI) is unknown [5]; the researchers, therefore, develop their method to exploit the information regarding WSI-level labels and ROI features. Multi-instance learning (MIL) is a popular solution in analyzing ROI features using WSI-level labels [5]. Such methodology enables further exploration in the pathology analysis as many characters encounter each other harmoniously.

1. Characters of pathology samples

In the analysis of pathology images, the condition is different from the computer vision field. Firstly, as a typical type of medical image data, data scarcity is the most pivotal problem. On

the one hand, the limited senior pathologists and the lack of valuable time made the precise annotation a tremendous expensive work [5]. Moreover, the detailed dataset may conflict with the patients' privacy. Therefore, the publicly available datasets are relatively small and usually without pixel-level annotation, which increases the difficulty in training models. Secondly, the medical images varying from different domains and pixel-size compared with the nature images, domain misalignment issue hinders the transfer learning method from performing its full potential [7]. Thirdly, the ROI-level images only have limited local features comparing slide-level samples, which lack cross-scale connection. In contrast, the WSI images contain tens of billions of pixels each [1], but the size made them hard to fit in the GPU video memory.

2. MIL in pathology

MIL is a learning method regarding the features between different samples in a bag, enabling the MIL models to model a bag together with only a bag-level label [5]. In practice, by dividing a WSI image into patches and regarding them a bag, the MIL models learn the features within each patch and model the bag-level information under the supervision of the bag-level (WSI-level) label [8]. The MIL method trained the model with the weak-label condition, for example, in [5], when training a network to observe the ROI-level tumor purity with only the tumor purity of WSI-level available. Compared with the split idea introduced in many works, which divide the WSI or ROI into patches and train them separately on regression or voting tasks, MIL exploits the general label of the bag and generates the between instance patterns while the detailed label of each patch is not available. Such an idea can support the pathology studies' learning strategy when only a WSI-level label is available. The recent trend of applying the cutting-edge Transformer into the pathology analysis shade light on other possibilities to model the general pattern between the samples [7,9], which may be a new method in the MIL modeling on WSIs.

3. A MIL example on tumor purity prediction

As an important indicator of cancer in the histopathology samples, tumor purity is predicted from H&E stained histopathology slides by the MIL model in [5]. With a novel distribution pooling module in [10], the authors create a MIL model dividing each sample as a bag of images, using the pooling module to obtain attention-aided features across the instances; and using the sample's genomic tumor purity as the bag label. Although without patch-level labels, the results in [5] show that the model has the ability to predict tumor purity accurately

across eleven different cohorts. Furthermore, the prediction of spatial tumor purity maps reveals the wilder benefit by applying MIL methods. The exciting findings regarding the sample position bias of pathologists may contribute to clinical research. Lastly, the inspiring abilities on tumor identification lay the foundation in clinical practice.

Conclusion and Recommendations

In conclusion, the MIL is a unique way of helping scholars deploy models with weak label conditions in pathology image analysis. In the datasets where only the WSI-level labels are available, the MIL method can help the model learn the cross-instance information among instances in a bag by taking the given labels as bag-level labels. The wilder application is expected as the MIL not only enables the model to obtain cross instance patterns but also makes the same model doing other relevant tasks possible. The application of MIL with Transformer may be expected in future studies as the bag-level labels encounter the multi-length bags (patches), which can be deployed as a deformable method across the different ROI scales within a WSI.

Reference

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