Subcategory Classifiers for Multiple-Instance Learning and Its Application to Retinal Nerve Fiber Layer Visibility Classification

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***Abstract*—We propose a novel multiple-instance learning (MIL) method to assess the visibility (visible/not visible) of the retinal nerve fiber layer (RNFL) in fundus camera images. Using only image-level labels, our approach learns to classify the images as well as to localize the RNFL visible regions. We transform the original feature space into a discriminative subspace, and learn a region-level classifier in that subspace. We propose a margin-based loss function to jointly learn this subspace and the region-level classifier. Experiments with an RNFL data set containing 884 images annotated by two ophthalmologists give a system-annotator agreement (kappa values) of 0.73 and 0.72, respectively, with an interannotator agreement of 0.73. Our system agrees better with the more experienced annotator. Comparative tests with three public data sets (MESSIDOR and DR for diabetic retinopathy, and UCSB for breast cancer) show that our novel MIL approach improves performance over the state of the art. Our MATLAB code is publicly available at https://github.com/ManiShiyam/Sub-category-classifiers-for-Multiple-Instance-Learning/wiki.**

***Index Terms*—Image classification, multiple-instance learning (MIL), retinal biomarkers for dementia, retinal image processing, retinal nerve fiber layer (RNFL).**

I. Introduction

THIS paper introduces an automatic system assessing the visibility and location of the retinal nerve fiber layer (RNFL) in fundus camera (FC) images from image-level labels. The optic nerve transmits visual information from the retina to the brain. The expansion of the neural fibers in the optic nerve enters the retina at the optic disc. It forms the RNFL, the innermost retinal layer (Fig. 1). The RNFL has been implicated in prediagnostic stages of glaucoma [1] and recently considered as a potential biomarker for dementia [2], by assessing its thickness in optical confocal tomography (OCT) images. However, screening of high numbers of patients would be enabled if the RNFL could be assessed with FC, still much more common than OCT for retinal inspection, already included in large, cross-linked data sets, and increasingly part of routine optometry checks. Some RNFL-related studies with FC images have been reported, mostly for estimating glaucoma risk [3], but there is very little work on studying associations with dementia with FC images [4]. This is in contrast with RNFL analysis via OCT, supported by a rich literature [2], [5]. The RNFL is not always visible in FC images, and its visibility itself has been posited as a biomarker for neurodegenerative conditions. This motivates our work, part of a larger project on multimodal retina–brain biomarkers for dementia [6].

We report an automatic system to identify FC images with visible RNFL regions and simultaneously localize visible regions. A crucial challenge is obtaining ground-truth annotations of visible RNFL regions from clinicians. Region tracing is notoriously a difficult and time-consuming process. We take therefore a multiple-instance learning (MIL) approach, requiring only image-level labels (RNFL visible/invisible), which can be generated much more efficiently. In MIL, images are regarded as *bags*, and image regions as *instances*. Each bag has an associated label, and the labels of its instances are unknown.

Visible RNFL regions have significant intraclass variations, and can be difficult to distinguish from other regions. To address this, we embed the instances in a discriminative subspace defined by the outputs of a set of subcategory classifiers. An instance-level (IL) classifier is then learned in that subspace by maximizing the margin between positive and negative bags. A margin-based loss is used to learn the IL and the subcategory classifiers jointly.

This paper brings two main contributions.

1) To the best of our knowledge, we address a new problem with significant impact potential for biomarker discovery, i.e., classifying FC images as RNFL visible/invisible, including region localization.
2) As shown in the experiments with a local (RNFL) and three public data sets, we improve the experimental performance compared to state-of-the-art MIL systems by proposing a novel MIL approach with a novel margin-based loss (instead of the cross-entropy loss commonly used in comparable MIL systems).

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