Development of multi-channel multiple instance based Deep Learning classifier for detection of diabetic retinopathy utilising Optical Coherence Tomography Angiography

Master's Thesis Proposal for MSc Data Science 066 645

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1 Motivation and Problem Statement

Diabetes Mellitus (DM) is one of the biggest public health crises in the developed world, with up to 700 million adults expected to suffer from the disease by 2045 in the OECD[1].

One of the complications of diabetes - Diabetic retinopathy (DR) - is the leading causes of blindness amongst the working-age population in Europe,[2] accounting for 51% of blindness cases worldwide and is prevalent in 34.6% of diabetic patients.[3]. High blood sugar levels (hyperglycaemia) cause damage to the capillary network in the retina which provides a constant supply of oxygen. As the damage to the vessels get worse, bleeding and a buildup of scar tissue leads to loss of vision.

As symptoms do not occur until the later stages of the disease, timely diagnosis is essential to prevent DR from deteriorating into vision loss. Most developed countries offer annual screening by an ophthalmologist, most commonly with fundus photography using an ophthalmoscope which produces a 2D surface image of the retina(refer Figure 1a). While it detects some DR biomarkers (specifically microaneurysms), these images are not able to show other biomarkers such as neovascularisations and oedemas.[4].

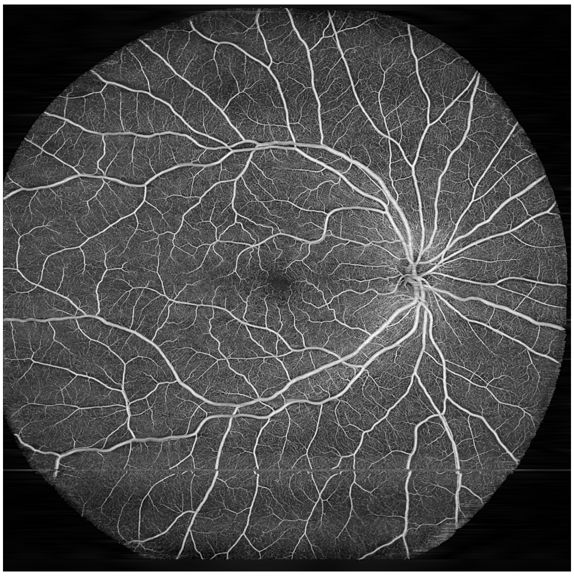
While other methods do exist, Optical Coherence Tomography Angiography (OCTA) is a relatively new *non-invasive* method to obtain 3D images which trained professionals can use to locate neovasculariosations and oedemas.[5] [6]. Due to the way OCTA is produced, one can not only use the 3D image (also known as C-scans, refer Figure 3), but also obtain longitudinal slices (also known as B-scans, refer Figure 2), or enface projections (refer Figure 1b).

However, in all these images, the requirement for trained ophthalmologists to assess the images as well as the long processing times required to generate the tomographic images create a major bottleneck, particularly as regular screening is crucial not only to prevent vision loss, but also unnecessarily invasive procedures to treat late-stage DR.[7]

Therefore, having a reliable ML classifier would be an invaluable decision support tool, particularly in a screening context and flagging images of patients who may require a trained ophthalmologist to provide a better look. With the previously mentioned bottlenecks in mind, the ideal ML classifier must also: -

1. Be comprehensive: able to classify DR vs. non-DR rather than just specific symptoms of DR

(a) Fundus photograph of a healthy right eye[8]



(b) OCTA enface image of a healthy right eye

Figure 1: Comparison of fundus and OCTA Images

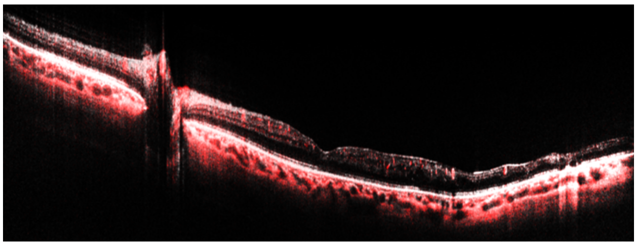


Figure 2: OCTA B-scan showing a longitudinal slice of the retina

2. Be easily trainable: i.e. does not require strongly-labelled* training data which requires a lot of effort from ophthalmologists

3. Minimise the need for using image data: if raw OCTA data can be used, then it would save the processing power and time needed to convert the data into the 3D images while also eliminating dependence on the quality of the image reconstruction process

As a step towards this goal of an ideal classifier, Philipp Matten and Julius Scherer at ZEISS Lab at Medical University of Vienna (MUW) led the development of MIL-ResNet14 (MIL-ResNet14), a multiple instance learning (MIL) classifier which successfully outperformed other state-of-the-art benchmark classifiers in classifying DR biomarkers from weakly-labelled OCTA enface (Refer Figure 1b) images†. This thesis aims to further build on this foundation.

2 Goals and Aim of the Work

The goal of this thesis is the next logical step to further build on Matten, Scherer et al.'s MIL-ResNet14 foundation, i.e. incorporating volumetric OCTA (C-scans) instead of the 2D enface images previously used. The evolved classifier will be evaluated on accuracy, F1-score, and area under the curve (AUC) and compared against the original MIL-ResNet14 classifier, the two benchmark classifiers used in

*In an OCTA context, well-labelled data which shows various lesions, their locations, and the relevant types

†As at the proposal submission deadline, the relevant conference paper has not yet been presented at the 2023 SPIE Image Processing Conference as Paper 12464-60. This paper will be correctly cited during the thesis submission

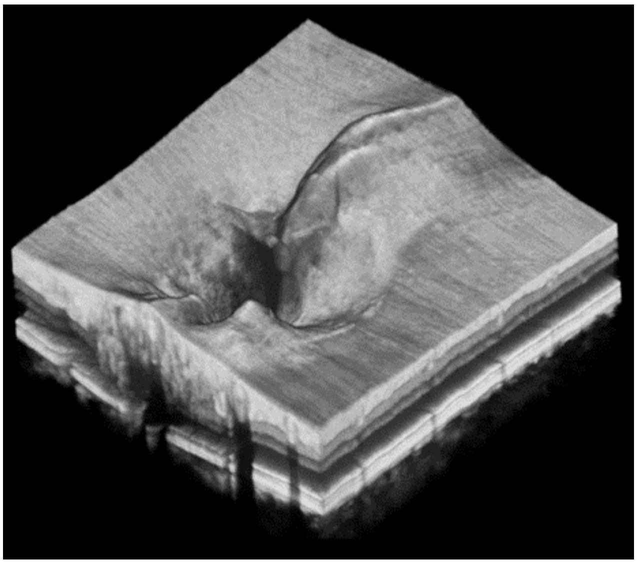


Figure 3: OCTA C-scan showing a 3D image of the retina

the previous work (Res-Net14 and VGG16), and any potential new state-of-the-art classifiers that may show up in the course of literature review.

If time permits, the intention is to make some headway into somehow incorporating raw OCTA data.

3 Methodology

3.1 Literature Review

The literature review will cover the following topics: -

- Basic Ophthalmological Knowledge
- Diabetic Retinopathy: Pathogenesis, Epidemiology, Diagnosis
- Prior Art of Retinal Imaging Methods
- Optical Coherence Tomography
- Overview of machine learning (ML) Usage in Medical Classification
- Multiple Instance Learning
- Prior Art of Classifiers Specifically Using Optical Coherence Tomography (OCT) as a Source

3.2 Data Acquisition and Initial Preprocessing

The dataset to be used consists of OCT scans of 102 diabetic patients with varying stages of DR and 40 healthy volunteers. In the previous work, the scans were processed into 2D enface images for the model to train on. This initial step will need to be conducted in order to reproduce previous work. In addition, we will also be using the same scans to generate 3D OCTA images to train the 'next-generation' model.

3.3 Reproduction of Prior Work and Benchmarks

As part of obtaining a deeper understanding of the current MIL-ResNet14 classifier, we intend to reproduce the previous work on the architecture on 2D en-face images. At the same time, we will build the benchmark models using the same architectures described in the previous paper.

For explainability, the Gradient-weighted Class Activation Mapping (Grad-CAM) visualisation which provides saliency maps which highlight areas in the image which played a large role in the network's decision will also be reimplemented. (Refer Figure 4)

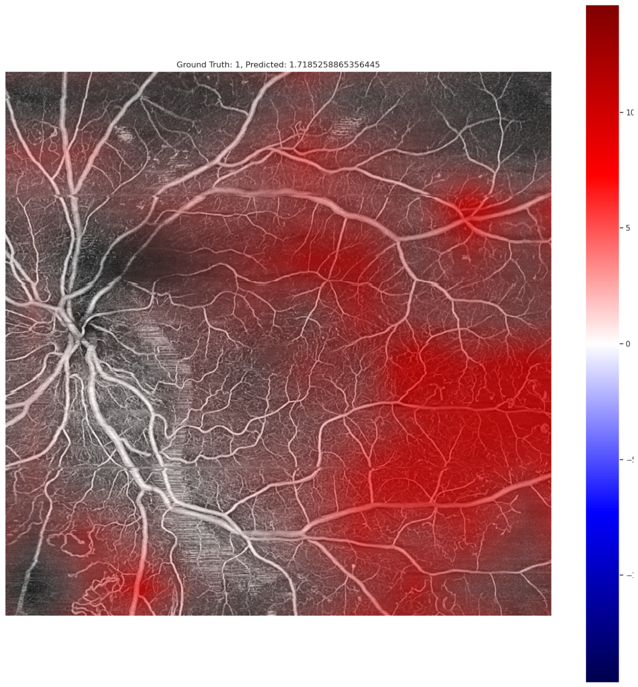


Figure 4: OCTA enface image with Grad-CAM saliency map showing important areas

3.4 Modelling

Following the reproduction, the new evolved model incorporating 3D images will be built and variations to the architectures and hyperparameters explored.

At the same time, if new benchmarks are discovered during Literature Review, these will also be implemented here.

3.5 Evaluation

As the data is weakly labelled, traditional methods of evaluating need to be reconsidered. To provide a stronger basis for evaluation, the test dataset will be individually graded by an eye clinician into four categories: healthy, diabetic with no signs of DR, mild signs of DR, and severe signs of DR. We will measure accuracy, F1-score, and AUC scores against this stronger-labelled grading.

In addition, the saliency maps from Grad-CAM will be analysed qualitatively to determine if the model focused on similar DR symptoms that a trained clinician would focus on.

3.6 Stretch Goals

If the aforementioned goals are achieved and time is still available, we will attempt to provide theoretical recommendations as to how the raw data can be incorporated, and also how one can improve explainability of such 'blackbox' models without the relevant image.

4 State of the Art

As discussed in the Problem Statement, the MIL-ResNet14 classifier we will be working on is arguably the state-of-the-art when it comes to OCT image classification, having beaten a published VGG16 transfer learning method which was the previous state-of-the-art.[9]

Prior to this, other deep learning approaches on OCT (as opposed to less-detailed fundus images) used included a Convolutional Neural Network (CNN) built by Ryu et al. which worked on a relatively small OCTA dataset of 240 images in total.[10] as well as a ResNet50-based approach and semi-supervised feature extraction approach against also less-detailed OCT B-scans. [11] [12]

In addition, Tilman Schmoll's group at the ZEISS Lab in MUW is one of the leading research groups in the ophthalmological field, particularly in OCT.

5 Relevance to the Curriculum

This work focuses on further development of an already-tried and novel Deep Learning (DL) algorithm in the field of Medical Image Processing. In addition to being bread-and-butter work for a Data Scientist, the following courses are relevant (directly or indirectly) to the work.

- Experiment Design for Data Science 188.992
- Machine Learning 184.702
- Data-intensive Computing 194.048
- Medical Image Processing VO 183.289
- Medical Image Processing UE 183.630
- Security, Privacy, and Explainability in Machine Learning 194.055
- Intelligent Audio and Music Analysis 194.039[‡]
- Epidemiological Methods 851.099/194.068

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[3] Ruhan Liu et al. "DeepDRiD: Diabetic Retinopathy—Grading and Image Quality Estimation Challenge". In: *Patterns* 3.6 (2022), p. 100512. ISSN: 2666-3899. DOI: `https://doi.org/10.1016/j.patter.2022.100512`. URL: `https://www.sciencedirect.com/science/article/pii/S2666389922001040`.

[‡] a lot of the signal processing work and Fourier transformations are relevant to the preprocessing required in OCTA images

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