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Risk assessment of diabetic retinopathy with machine and deep learning models with PPG signals and PWV

Serena Zanelli¹ and Kornelia Eveilleau², Mehdi Ammi¹, Magid Hallab⁴, Mounim A. El Yacoubi⁵

Abstract—Retinopathy is one of the most common microvascular impairments in diabetic subjects. Elevated blood glucose leads to capillary occlusion, provoking the uncontrolled increase in local growth of new vessels in the retina. When left untreated, it can lead to blindness. Traditional approaches for retinopathy detection require expensive devices and high specialized personnel. Being a microvascular complication, the retinopathy could be detected using the photoplethysmography (PPG) technology. In this paper we investigate the predictive value of the pulse wave velocity and PPG signal analysis with machine and deep learning approaches to detect retinopathy in diabetic subjects. PPG signals and pulse wave velocity (PWV) showed promising results in assessing the diabetic retinopathy. The best performances were scored by a LightGBM based model trained over a subset of the available dataset obtaining 80% of specificity and sensitivity.

Clinical relevance— PPG based retinopathy detection could make the retinopathy detection more accessible since it does not need neither expensive devices for signal acquisition nor highly specialized personnel to be interpreted.

I. INTRODUCTION

Diabetes mellitus is a clinical condition that causes a high amount of glucose in the blood with a simultaneous lack of insulin or insulin resistance [5]. As stated by the World Health Organization, about 422 million people have diabetes and 1.5 million deaths are directly attributed to diabetes each year [16]. Retinopathy is the most common vision impairment in diabetic subjects [9]. Elevated blood glucose leads to capillary occlusion, provoking the uncontrolled increase in local growth of new vessels in the retina (Figure ?? - b). When left untreated, it can lead to blindness.

Traditional approaches used to detect the diabetic retinopathy can be fluorescent angiography, angiography, optical coherence tomography and ocular ultrasound [15]. All these methods require highly specialised personnel to be interpreted and expensive devices that can be found only in well equipped medical centers. Since diabetic retinopathy is a micro-vascular alteration, photoplethysmography (PPG) may be used to detect it. Thanks to its cost-effectiveness, it could be employed to perform large scale preventive analysis. In addition, PPG does not require a medical center in order to be acquired. It can be easily embedded in smartphones and wrist bands [2]. Thanks to its richness in cardiovascular information, researchers have been capable to use the PPG

signal to estimate blood pressure [6], arterial stiffness [3] and detect diabetes [18]. To the best of our knowledge, only one study has assessed the diabetic retinopathy through PPG analysis. Liao et al. [10] propose the harmonic analysis of PPG and radial pulse signals to detect retinopathy. They found that the fourth and third harmonic components may predict the risk of this complication in type 2 diabetic subjects.

In this paper, we have tested several machine learning and deep learning approaches with respect to the gold standard EyeArt AI system. We assess the capability of our models to detect the diabetic retinopathy using (i) biophysics data (such as blood test data) and clinical data, (ii) only clinical data (iii) or directly from the PPG waves only. The employed machine learning methods are: logistic regression (LR), support vector classifier (SVC), random forest (RF) and gradient boosting machine (lightGBM and XGBoost). To directly model the PPG signals, we employed convolutional neural networks (CNN). In order to improve the CNN performances, we used transfer learning techniques. We employed the weights of a pre-trained model trained over PPG waves to detect the signal quality [19] and we performed transfer learning to test the model on the diabetic retinopathy dataset. Secondly, we assessed the capability of transfer learning techniques to improve the classification performances. Our contributions can be summarized as follow:

- We propose a system to assess the risk of diabetic retinopathy in diabetic subjects using the PPG signal. We test machine learning handcrafted feature based and deep learning automatic feature based approaches trained over different sets of data and the raw PPG signal itself respectively. We perform a systematic comparison of the obtained results with respect to the EyeArt AI System for diabetic retinopathy screening.
- We utilize transfer learning to assess the possible benefits of using firstly a pre-trained model over a larger dataset and then fine tuning it to classify the diabetic retinopathy. The pre-trained model is a CNN model trained to assess the PPG wave quality [19].

The rest of the paper is organized as follows. In Section 2, we present the used protocol to collect data then we present the used databases and the models architecture. In Section 3, the results are presented. Finally, in Section 4, we conclude and discuss future work.

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II. METHODOLOGY

A. Retinopathy and pulse wave velocity

The finger to toe pulse wave velocity (PWV) is defined as the time difference between the systolic peak measured at the finger and the toe divided by the height of the subject (Figure 2). PWV is used clinically as a measure of the arterial stiffness. It is associated with the duration of diabetes and with the accumulation of fluorescent advanced glycation end products (AGEs) [1]. Several reports indicate that the stage of diabetic retinopathy correlates with the accumulation of AGEs [11]. Therefore, there is a possibility that the diabetic retinopathy is associated with PWV through the accumulation of AGEs [13].

B. Protocol

The used dataset is composed of subjects with type 1 and type 2 diabetes. The dataset has been collected at Centre for Diabetes and Endocrinology (CDE), Johannesburg, Gauteng, South Africa. For this study two non-invasive devices have been used. A Fundus photography camera linked to the EyeArt AI system for interpretation [7] and the pOpmetre device [12] for the measure of the PWV. The EyeArt AI system analyses the fundus photograph and provides a score from 0 to 4 indicating the diabetic retinopathy severity using the ICDR scale. A score equal to zero results in no detected retinopathy, while scores 1,2, 3 and 4 refer to mild non proliferative diabetic retinopathy (NPDR), mild NPDR, severe diabetic retinopathy and proliferative retinopathy respectively. pOpmetre sensors are placed on a finger and a toe on the same side of the body with the subject reclining. PPG signal is acquired during 12 seconds. From the finger and toe PPG signals, the pOpmetre device computes the PWV enabling interpretation of arterial stiffness and arterial age. Subjects with any history of any cardiovascular event were excluded from the protocol.

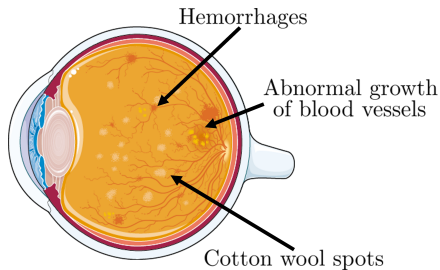


Fig. 1. Representation of a fundus photography with diabetic retinopathy.

C. Dataset

Before training the models, we performed an exploration data analysis in order to clean the dataset and remove the correlated features. The final dataset is composed of 81 subjects with retinopathy (score 1,2,3 and 4 from EyeArt AI system) and 46 subjects without retinopathy (score zero from the EyeArt AI system). All the 127 subjects are diabetic (type 1 and type 2). For each subject, we selected 14 features: age, gender, diabetes duration, weight, height, smoking (y/n), statin (y/n), hypertension (y/n), PWV, glycated

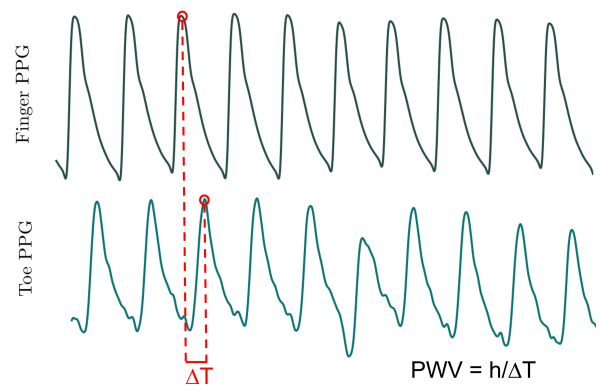


Fig. 2. Finger and toe PPG signals. ΔT : time between finger PPG systolic and toe PPG systolic peaks. h : subject's height, PWV: pulse wave velocity.

hemoglobin (HbA1c), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG) and diabetes type. Mean and standard deviation values of all the used features are reported into Table I.

TABLE I
DATABASE DESCRIPTION

Features	Non DR subjects (n=46)			DR subject (n=81)		
	Mean	Min	Max	Mean	Min	Max
Age	49.9 ± 13.3	20	72	49.1 ± 16.1	20	77
Duration	16.9 ± 11	2	53	25.4 ± 9.2	5	49
Weight	83.2 ± 17.5	43	139	81.8 ± 15	51	119.6
Height	170.1 ± 8.6	151	186	172.6 ± 8.8	153	195
PWV	8.1 ± 2.1	4.5	16.6	9.1 ± 3.3	4.6	19.2
HbA1c	7.8 ± 1.8	5.3	15.5	7.7 ± 1.1	6.1	11.5
LDL	2.3 ± 0.7	0.6	4.1	2.2 ± 0.8	0.5	4.8
HDL	1.4 ± 0.5	0.7	3	1.6 ± 0.5	0.8	3.1
TG	2.2 ± 1.8	0.6	8.5	1.4 ± 0.9	0.4	5.1
DT1	n=22			n=57		
DT2	n=24			n=24		
Statin	n=22			n=39		
HP	n=18			n=31		
Smoking	n=7			n=11		

DR: diabetic retinopathy. Age[years], Duration[years], Weight[kg], Height[cm], PWV[m/s], HbA1c[%], LDL[mmol/L], HDL[mmol/L], TG[mmol/L]

In order to train the CNN model, we created a dataset composed of single raw PPG waves. The PPG signals belonging to the analysed subjects have been filtered and segmented into individual waves using the second derivative peak and the PPG local minimum after the diastolic peak. PPG waves are normalized in time and amplitude. The datasets are splitted into train and test using 70% and 30% of the available data respectively. One subject can appear only in training or tests ensuring the correct data separation. The PPG wave dataset and the feature dataset used the same split of subjects in train and test.

D. Machine learning

In order to assess the risk of diabetic retinopathy in diabetic subjects, we trained, optimized and tested the following machine learning models: logistic regression (LR), support vector classifier (SVC), random forest (RF) and gradient boosting machine (lightGBM and XGBoost). The latter

have been optimized using the GridSearch method. Since the absence/presence retinopathy classes are unbalanced we tested four different options. First we trained and tested the models using unbalanced classes, then we employed the weighted classes to penalize misclassifications from the minority class. In addition, we performed undersampling by randomly removing samples from the most populated class and, ultimately, oversampling using the synthetic minority oversampling technique (SMOTE) with the number of nearest neighbor $k = 2$. The models have been trained and tested over all the selected features and also over a reduced set of features removing all the blood test related features. The rationale behind the latter experiment is to assess the models' performances in assessing the diabetic retinopathy without using data that require expensive equipment and specialized personnel (such as blood tests). Models are cross-validated over $j = 5$ folds.

E. Deep learning

To directly model the PPG signals, we tested a deep learning model that does not require handcrafted feature extraction. The model consists of four convolution layers, followed by a fully connected layer. Each convolution layer is followed by a maxpooling layer. The output of the maxpooling layer is a set of feature maps containing the most prominent features of the previous feature maps. A flattening layer is added after the last convolution layer in order to pass the feature maps to the fully connected layer. Relu activation functions have been used for the convolution layers, while a sigmoid activation function has been used for the classification layer. The network parameters are optimized with the Adam method, and binary cross-entropy is used as loss function in the output layer. To mitigate the unbalanced class effect, we tested the model either by considering the class weights in the loss function or undersampling the most populated class. We optimized the CNN models hyperparameters using Autonomio Talos tool. In order to assess the efficiency of transfer learning techniques to enhance classification performances we fine tune a pre-trained CNN model. The pre-trained model is a model for PPG quality assessment (CNN_SQI) [19]. We performed fine tuning by training the CNN_SQI replacing the last dense layer with a new non-trained layer. The model is trained and tested with the unbalanced dataset, the undersampled dataset and with class weights.

III. RESULTS AND DISCUSSION

In this section we present and discuss the results obtained in detecting diabetic retinopathy with the proposed models. In order to globally evaluate the models performances, we computed the positive predicted values (PPV), the negative predictive value (NPV), the sensitivity, the specificity, the area under the curve (AUC) and the f1 score for each tested model.

A. Machine learning with all the dataset

We present in this paragraph the results obtained with machine learning models trained over the whole available

features. The performance analysis obtained over the test set is reported into Table II. The best performances were obtained by the Random Forest algorithm on the unbalanced dataset (without weighting scheme) and from the LightGBM with the oversampled dataset. RF scored a lower specificity, meaning that the model does not have a strong capability in detecting true negatives. LightGBM scored lower sensitivity and NPV but it performed the detection of true negative (specificity) with an accuracy of 0.73. In order to understand the impact of the PWV on the detection of the diabetic retinopathy we performed the feature importance analysis for the most performing models. For RF the PWV is the second most important feature after the diabetes duration. HbA1c, the gold standard to diagnose diabetes, is the sixth more important feature out of fourteen total features. For the LightGBM model, the PWV is the fifth most important feature. The most important feature is age.

TABLE II
MODEL PERFORMANCES FOR DIABETIC RETINOPATHY DETECTION WITH FULL DATASET

Unbalanced data						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
LR	0.74	0.73	0.87	0.53	0.70	0.80
SVC	0.78	0.67	0.78	0.67	0.72	0.78
RF	0.78	0.82	0.91	0.60	0.76	0.84
LightGBM	0.76	0.89	0.96	0.53	0.75	0.85
XGboost	0.73	0.67	0.83	0.53	0.68	0.78
Weighted classes						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
LR	0.70	1.0	1.0	0.33	0.67	0.82
SVC	0.67	0.55	0.78	0.40	0.59	0.72
RF	0.73	0.88	0.96	0.47	0.71	0.83
LightGBM	0.61	0.0	1.0	0.0	0.50	0.75
XGBoost	0.75	0.56	0.65	0.67	0.66	0.70
Undersampling						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
LR	0.67	0.67	0.67	0.67	0.67	0.67
SVC	0.65	0.69	0.73	0.60	0.67	0.69
RF	0.69	0.65	0.60	0.73	0.67	0.64
LightGBM	0.54	0.53	0.47	0.60	0.53	0.50
XGboost	0.64	0.63	0.60	0.67	0.63	0.62
Oversampling						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
LR	0.76	0.59	0.70	0.67	0.68	0.73
SVC	0.61	0.0	1.0	0.0	0.50	0.75
RF	0.74	0.60	0.74	0.60	0.67	0.74
LightGBM	0.83	0.73	0.83	0.73	0.78	0.83
XGboost	0.73	0.67	0.83	0.53	0.68	0.78

PPV: positive predicted value, NPV: negative predicted value, AUC: area under the curve, f1: f1 score. LR: logistic regression, SVC: support vector classification, RF: random forest, LightGBM: light gradient-boosting machine, XGBoost: eXtreme gradient boosting.

B. Machine learning with partial dataset

In this paragraph we present the results obtained with the machine learning models trained over a reduced dataset. We selected only the features that do not require an invasive measure. The objective is to assess the capability of the model to predict the diabetic retinopathy with data that are easy to access. The used features are: age, diabetes duration and type, gender, weight, height, statin, hypertension,

TABLE III

MODEL PERFORMANCES FOR DIABETIC RETINOPATHY DETECTION WITH PARTIAL DATASET

Unbalanced data						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
LR	0.73	0.88	0.96	0.47	0.71	0.83
SVC	0.75	0.64	0.78	0.60	0.69	0.77
RF	0.74	0.73	0.87	0.54	0.70	0.80
LightGBM	0.74	0.60	0.74	0.60	0.67	0.74
XGBoost	0.76	0.69	0.83	0.60	0.71	0.79
Weighted classes						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
LR	0.72	1.0	1.0	0.40	0.70	0.84
SVC	0.64	0.46	0.70	0.40	0.55	0.67
RF	0.76	0.89	0.96	0.53	0.74	0.85
LightGBM	0.61	0.0	1.0	0.0	0.50	0.75
XGBoost	0.76	0.70	0.83	0.60	0.71	0.79
Undersampling						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
LR	0.68	0.82	0.87	0.60	0.73	0.77
SVC	0.75	0.79	0.80	0.73	0.77	0.77
RF	0.67	0.75	0.80	0.60	0.70	0.73
LightGBM	0.80	0.80	0.80	0.80	0.80	0.80
XGBoost	0.71	0.77	0.80	0.67	0.73	0.75
Oversampling						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
LR	0.71	0.53	0.65	0.60	0.63	0.68
SVC	0.74	0.53	0.61	0.67	0.64	0.67
RF	0.73	0.56	0.70	0.60	0.65	0.71
LightGBM	0.73	0.56	0.70	0.60	0.65	0.71
XGBoost	0.76	0.70	0.83	0.60	0.71	0.79

PPV: positive predicted value, NPV: negative predicted value, AUC: area under the curve, f1: f1 score. LR: logistic regression, SVC: support vector classification, RF: random forest, LightGBM: light gradient-boosting machine, XGBoost: eXtreme gradient boosting.

smoking and PWV. Overall, the performances (Table III) are comparable to the results obtained over the full dataset. The LightGBM approach outperformed the others with a sensitivity and a specificity equal to 80%. The PWV turns out to be the fourth most important feature.

C. Deep learning with raw PPG waves

In this paragraph we present the results obtained by training the CNN model with raw PPG waves as input in order to detect diabetic retinopathy (Table IV). Overall, the proposed method did not outperform the machine learning methods trained over the total dataset. The best performances were scored using transfer learning. In particular, when the pre-train model CNN_SQI has been trained over the unbalanced dataset.

IV. CONCLUSION

This study aims to evaluate the predictive value of PPG signals and PWV to assess the risk of retinopathy in diabetic subjects. Although further studies are needed, the proposed approaches showed promising results. In particular, RF and LightGBM models were able to perform decently when trained over the full dataset and on the undersampled dataset respectively. The diabetes duration has been evaluated as the most important feature in the RF approach. This result is consistent with the fact that this vision impairment seems to not be present in the early stages of the pathology

TABLE IV

CNN PERFORMANCES

Unbalanced data						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
CNN	0.61	0.43	0.83	0.20	0.51	0.70
CNN SQI TL	0.73	0.56	0.70	0.60	0.65	0.71
Undersampling						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
CNN	0.50	0.21	0.52	0.20	0.36	0.51
CNN SQI TL	0.71	0.48	0.52	0.67	0.60	0.62
Weighted classes						
Model	PPV	NPV	Sensitivity	Specificity	AUC	f1
CNN	0.62	0.42	0.70	0.33	0.51	0.65
CNN SQI TL	0.64	0.44	0.61	0.47	0.54	0.62

PPV: positive predicted value, NPV: negative predicted value, AUC: area under the curve, f1: f1 score. CNN: convolutional neural network trained for diabetic retinopathy detection, CNN_SQI TL: CNN_SQI model fine tuned for diabetic retinopathy detection.

[17]. Nonetheless, PWV, when modeled by the RF algorithm, appears to be the second most important feature. The LightGBM approach selected the diabetes type as the most important feature. Also in this case, this result is consistent with the fact that diabetic retinopathy seems to have a different incidence for diabetes types [14]. Different ranks of feature importance can be justified by the different performances of the models. The proposed models employed the features in a different manner one from the other.

Future improvement will focus on augmenting the dataset used to train the CNN model by generating new data with generative methods such as GANs [8]. In addition, the CNN approach could be further explored injecting handcrafted PPG features and subjects related data inside the network. Since the detection of the diabetic retinopathy is a clinical application, particular attention should be paid also to the model interpretability [4]. In addition to that, we will further explore our approaches by assessing the PWV and PPG predictive value to detect diabetic retinopathy in type 1 and type 2 diabetic subjects separately.

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