Multiple Modality Fusion for Glaucoma Diagnosis

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Abstract— **Computer-aided diagnosis for diagnosis / screening makes use of artificial intelligence based analytical methodologies to handle patient data. Ocular disease Glaucoma is the major irreversible cause of blindness. Past works focus on building systems on single modality (personal data or major image features) and achieve limited success. At this time, there isn't an effective and standard screening practice, which leads to more than half of the glaucoma cases are undiagnosed, which prevents the early treatment of the disease and is a big burden to the patients and health management.**

Overcoming the limitation of the performance of single modality based system, a multiple modality fusion based glaucoma diagnosis approach is introduced and discussed in the paper by integrating patient personal data, major ocular image features, and important genome SNPs features in one system. Multiple kernel learning is used to integrate the features from different modalities; different kernel functions correspond to different modalities of the integrated data and therefore are treated as different aspects of similarity. 2,258 cases from a Singapore population study are tested and evaluated the multiple modality fusion based glaucoma diagnosis approach. Receiver Operating Characteristic curves are plotted to compare the approach's performance with individual classifiers based on patient personal data, images, and genome SNPs separately. Instead of using the cross-validation Leave-One-Out approach, which may prone to statistical over-training, this paper separates the training and testing dataset and gives a convincing analysis of the performance of the approach. This new testing approach clearly shows that the multiple modality fusion based glaucoma diagnosis approach is able to achieve an area under curve value better than the individual personal data, image and genome information components respectively.

Keywords— **Multiple modality fusion, medical imaging informatics, glaucoma diagnosis and screening, early detection, multiple kernel learning.**

I. INTRODUCTION

Glaucoma is an eye disease, in which high fluid pressure or some other factors within the eye results in damages to the delicate fibers of the optic nerve. These delicate nerve fibers are responsible for carrying visual impulses from the eye to the brain. In glaucoma, the death of the optic nerve fibers can lead to irreversible loss of vision, culminating in blindness in advanced cases[1]. Based on surveys conducted by the World Health Organization, glaucoma has been found to be the second leading cause of blindness worldwide. By 2020, the disease will affect up to 80 million people. [2].

Unlike other eye diseases, glaucoma is usually asymptomatic in the early stages. The pattern of vision loss in glaucoma begins at the peripheral vision and gradual vision loss occurs inwards from the periphery. Due to the complementary nature of the two eyes in the human visual system and the capability of the brain to fill in gaps in vision loss, early glaucoma in one eye is seldom noticeable by the subject. When vision loss has occurred to the extent in which it is noticeable by the subject, substantial visual loss has already occurred. This has given rise to its nickname as the 'silent thief of sight'. Loss of vision in glaucoma can be more than 60% in five years if left untreated[3].

Due to the irreversibility of vision loss in glaucoma, there is strong clinical and economic impetus to detect the disease in as early a stage as possible to control progression of the disease and to save sight. Clinical intervention on detection depends on the type and severity of glaucoma and it may be in the form of medication, laser therapy or surgery. Such measures have been shown to be effective in slowing or halting progression.

However, due to lack of medical doctors and effective way of mass screening, studies in Singapore and other countries have shown that up to 90% of glaucoma cases remain undetected in the population [4,5].

There are many ways to detect glaucoma [6]. Traditionally, glaucoma can be detected from raised intraocular pressure (IOP) and visual field loss. IOP measurements usually require the use of air puff or Goldman tonometers to measure the pressure within the eyeball, which visual field assessments require the use of visual field perimetric instruments. Recently, assessment of the damaged optic nerve has been demonstrated clinically to be more accurate than IOP measurement or visual field testing. This is also in line with the fact that the optic nerve damage precedes vision loss and can be used to detect glaucoma earlier with higher sensitivity. Ocular image-based optic nerve assessment can be performed by trained glaucoma specialists. However, as such a manual assessment is subjective, time consuming and expensive, there remains a strong need for an efficient

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and objective way to screen for glaucoma. Clinically, the American Academy of Ophthalmology and many national academies have strongly recommended screening for glaucoma as part of comprehensive adult medical eye evaluation, with screening frequency depending on an individual's age and other glaucoma risk factors. In reality, this is very difficult due to the lack of glaucoma specialists and the high cost associated with it.

II. MULTIPLE MODALITIES FOR GLAUCOMA DIAGNOSIS AND SCREENING

Personal data and other ocular measurements have been used to develop models of prediction for glaucoma [7,8], however, these models not only suffer from low accuracy but also use input parameters obtained from highly specialized instruments found in tertiary care institutions, which may not be suitable or readily available for screening.

Computer-aided diagnosis for diagnosis/screening makes use of artificial intelligence based analytical methodologies to handle patient data. Glaucoma is the one of the major irreversible causes of blindness. Past works focus on building systems using a single modality (personal data or major image features) and have achieved limited success. At this time, there is no effective and standard screening practice. More than half of the glaucoma cases are undiagnosed, which prevents the early treatment of the disease and is a big burden to the patients and health management.

To overcome the limitations of designing the diagnosis system from single modality, we look at this issue from the medical image information domain. Data in medical informatics can be broadly classified as personal data, imaging data and genetic data modalities. In the "big data" era, data mining and informatics technologies have been widely used in biomedical and medical imaging [9]. Understanding and interpreting the complex relationships of the data from various modalities is a challenge in computer aided diagnosis.

A multiple modality fusion based glaucoma diagnosis approach is introduced and discussed in this paper by integrating patient personal data, major image features, and important genome SNPs features into one system. Multiple kernel learning is used to integrate the features from different modalities; different kernel functions correspond to different modalities of the integrated data and therefore are treated as different aspects of similarity. 2,258 cases from a Singapore-based population study [4] are used to test and evaluate the proposed approach. Receiver Operating Characteristic curves are plotted to compare the performance of the multiple modality fusion based glaucoma diagnosis with classifiers using patient personal data, images, and genome SNPs separately. Instead of using the Leave-One-Out approach, this paper separates the training and testing dataset and gives a convincing analysis of the performance of the approach, which clearly shows that the multiple modality fusion based glaucoma diagnosis approach is able to achieve an area under curve value better than the individual personal data, image and genome information components respectively.

III. MULTIPLE MODALITIES FUSION FOR GLAUCOMA DIAGNOSIS

The rapid development of medical imaging informatics offers new insights into the computer-aided diagnosis of diseases. Integrating automatic medical image analysis with the utilization of informatics methodologies from patient personal data text modality, imaging modality and genome SNPs modality offers an innovative way for glaucoma disease diagnosis.

AGLAIA-MII [10] is a framework for multiple feature integration. Based on the same principle, multiple modality fusion based glaucoma diagnosis approach in this paper (as shown in Fig. 1) fuses features from three modalities, namely a subject's personal data, imaging information from ocular fundus image, and patient's genome information.

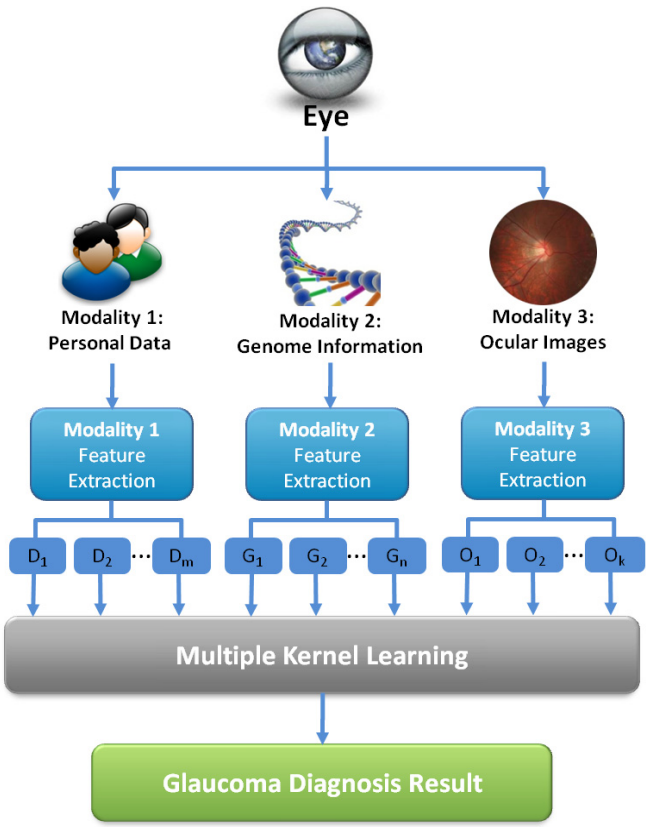

Fig. 1: Multiple modality fusion framework for glaucoma diagnosis.

Features from each modality modalities are analyzed separately first. Subsequently, these features from different modalities are passed to a Multiple Kernel Learning (MKL) based fusion framework to diagnosis glaucoma.

The eye data [4] is threaded into 3 modalities: the personal data modality 1 includes 46 variables for any given subject; 178 SNPs are used as genetic features in modality 2 for glaucoma assessment; 569 dimensional features are selected from modality 3.

The personal data modality contains demographical data include simple data like age, gender and height; it also includes ocular examination data by clinicians including intro-ocular pressure (IOP) and cornea thickness; historical medical records are also included for better diagnosis. Ocular images are acquired using a 45° FOV Canon fundus camera with a 10D SLR backing, 3,072 × 2,048 pixel resolution is set for the Canon camera. Illumina 610quad arrays are used to obtain the genotypes from the subjects. From the large dimensional genotyping data which contains more than 500K SNPs, we selected 178 glaucoma-associated SNPs identified in [11] as genomic features. To make the diagnosis more authoritative, glaucoma specialists are engaged to conduct the clinical ground truth marking for the glaucoma diagnosis.

Multiple kernel learning (MKL) [12] is used in the paper to train the classifier. In this approach, given p pre-learned base kernels $K_1, K_2, \cdots, K_p$ that are potentially well suited for a sub problem, we are to find a linear combination of these kernels such that the resulting linear combined kernel $\mathrm{K} = \sum_{i=1}^{p} d_i K_i$ is "optimal", where $\sum_{i=1}^{p} d_i = 1$, using the SLEP toolbox [13].

IV. EXPEIMENT

To verify that the fusion of multiple modalities can enhance the diagnostic accuracy of glaucoma, we report and compare the diagnostic performance of seven different combinations of three modalities:

(1) Personal data modality (referred to as M1);
(2) Genetic info modality (referred to as M2);
(3) Ocular image modality (referred to as M3);
(4) Personal data modality and genetic info modality (referred to as M1 + M2);
(5) Personal data modality and Ocular image modality (referred to as M1 + M3);
(6) Genetic info modality and Ocular image modali ty (referred to as M2 + M3);
(7) Personal data modality. Genetic info modality and Ocular image modality (referred to as M1 + M2 + M3).

2,258 samples from the Singapore Malay Eye Study (SiMES) database [4] are used for the experiment, which are equally divided into two folds. Each fold includes 50 glaucoma (positive) cases and 1,079 normal (negative) cases.

For an unbiased and non-overlap training and test, the first fold is used for training and the other is used for testing. In the training, different weights are assigned to positive and negative samples, to guarantee that positive and negative samples have equal weight sum, this is to overcome the imbalance of the data distribution.

Sensitivity and specificity are both calculated in our tests. Sensitivity is defined as the proportion of glaucoma cases that are correctly identified by the test. Specificity refers to the proportion of true negatives which are correctly determined by the test. To obtain the overall diagnostic performance of each combination, we plotted the receiver operating characteristic curve (ROC) from paired values of sensitivity and sensitivity, and calculated the area under the curve (AUC) values for each combination.

Fig. 2 shows the AUC values of different combination of modalities for glaucoma diagnosis. AUC for M1+M2+M3 is the highest (0.869 compared to other combinations), while the AUC for M2+M3 is the second highest, at 0.859. M2 is the key contributor for the AUC performance (AUC for M2 is 0.848, while AUCs for M1+M2 is 0.857 and that of M2 + M3 is 0.859). The results show that the fusion of all three modalities consistently performs better than that of the individual classifiers. Fig. 3 shows the ROC curves of different combination of modalities for glaucoma diagnosis.

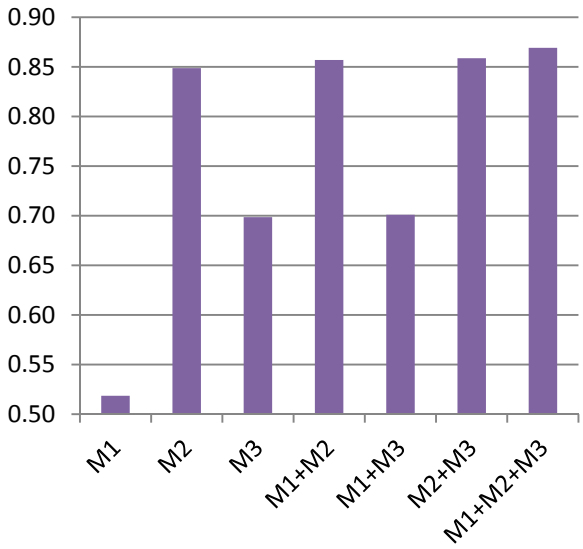

Fig. 2: The AUC comparisons of different combination of modalities for glaucoma diagnosis.

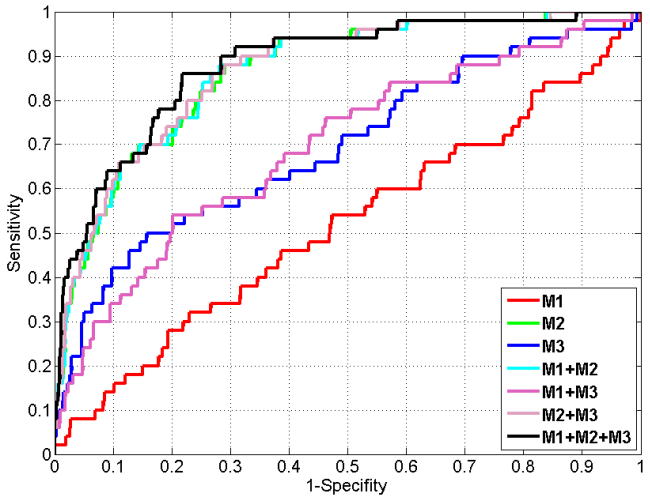

Fig. 3: ROC curves of different combination of modalities for glaucoma diagnosis.

V. Discussions

To enhance the detection of glaucoma from that of a single modality based system, we have presented a multiple modality fusion based glaucoma diagnosis in this paper. The approach is further verified on a large population database by fusing the different modalities namely, personal data modality, ocular image modality, and genome SNP modality through multiple kernel learning.

As statistical over-training has been questioned by using the cross-validation Leave-One-Out approach, we conduct a straight two-fold (separation of the training and testing sets) in order to obtain better evaluation of the proposed method.

Standard ROC curves analysis is used to compare the performance of the proposed approach with that of individual classifiers based on individual modalities. The AUC and ROC plots show that fusion of all three modalities results in a consistently better performance.

VI. Conclusions

As the number of older adults explodes globally and especially in the developing countries, it is both an ethical responsibility and a public health imperative to prevent avoidable vision loss. Early diagnosis of glaucoma is one of the key tasks. Governments worldwide have a keen interest to prevent vision loss, which is seen as an investment that facilitates social and economic engagement of ageing populations. This creates cost savings for both individuals and health systems when ocular diseases are discovered and treated earlier.

An effective diagnosis/screening program is in high demand and researchers have investigated various methods to boost the performance of automatic systems to meet the society needs. The use of artificial intelligence based analytical methodologies to handle multiple modalities of patient data has been demonstrated as a promising way to address this challenge.

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