INNOVATIONS IN PEDIATRIC RETINAL DISEASE DIAGNOSIS AND UNVEILING THE GENETIC LANDSCAPE

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ABSTRACT:

In children, inherited retinal diseases (IRD) can lead to severe vision problems and even blindness. Diagnosing these diseases is challenging due to numerous genetic causes and complex clinical tests, often invasive and unsuitable for young patients. To address this, a novel approach utilizing Chromatic Pupillometry, a technique assessing outer and inner retina functions, was developed. A unique Clinical Decision Support System (CDSS) based on Machine Learning and combining hardware (pupillometer) and software was created. The CDSS, employing two Support Vector Machines (SVMs) for each eye, successfully diagnosed Retinitis Pigmentosa in pediatric subjects. The system demonstrated an accuracy of 84.6%, sensitivity of 93.7%, and specificity of 78.6%. This groundbreaking study is the first to apply machine learning to pupillometric data for diagnosing genetic diseases in children. On a broader scale, a separate study aimed to understand the genetic basis of IRD, a significant cause of global blindness. Through exome sequencing of 179 Chinese families with IRD, 124 mutations in known retinal disease genes were identified, including 79 novel mutations (detection rate of 55.3%). The study revealed new genotype–phenotype correlations, highlighting the diverse genetic landscape of IRD. Notably, the identification of AHI1 as a novel candidate gene for nonsyndromic retinitis pigmentosa expanded the understanding of these diseases. This comprehensive exploration of genetic defects enhances our knowledge of IRD's phenotypic and genotypic heterogeneity, providing valuable insights for clinical diagnoses and personalized treatments.

INTRODUCTION:

Inherited degeneration (e.g. congenital glaucoma, dominant optic atrophy, Leber hereditary optic neuropathy). Both conditions are characterized by extremely high genetic heterogeneity with over 200 causative genes identified to The associate editor coordinating the review of this manuscript and approving it for publication was Asad Waqar Malik . date, which represent a remarkable obstacle to a rapid and effective diagnosis (https://sph.uth.edu/retnet/disease.htm), also considering that the same gene could cause different and heterogeneous clinical phenotypesRetinal Diseases (IRDs) represent a significant cause of severe visual deficits in children [1]. They frequently are cause of blindness in childhood in Established Market Economies (1/3000 individuals). IRDs can be divided into diseases of the outer retina, namely photoreceptor degenerations (e.g., Leber Congenital Amaurosis, Retinitis Pig- mentosa, Stargardt disease, Cone Dystrophy, Acromatopsia, Choroideremia,

etc.), and diseases of the inner retina, mainly retinal ganglion cell.

LITERATURE SURVEY:

A novel Clinical Decision Support System (CDSS) utilizing Machine Learning and Chromatic Pupillometry has been developed to aid in diagnosing Inherited Retinal Diseases in children. With over 200 causative genes and complex diagnostic challenges, this approach offers a promising alternative to invasive tests. The system combines a dedicated pupillometer with custom machine learning algorithms, specifically utilizing Support Vector Machines (SVMs) for each eye. Tested on pediatric subjects with Retinitis Pigmentosa, the CDSS achieved promising results with 0.846 accuracy, 0.937 sensitivity, and 0.786 specificity. This marks the first application of machine learning to pupillometric data for diagnosing genetic diseases in children.
Pupillometry, a non-invasive method measuring pupil size in response to light stimuli, was tested on children and adults with various diseases. Results demonstrated its effectiveness in accurately distinguishing between healthy individuals and those with diseases, achieving a sensitivity of 90% and specificity of 86%. This suggests pupillometry's potential as a tool for detecting genetic diseases in pediatric patients.

EXISTING SYSTEM :

'machine learning" and "eye diseases". The number of studies decreases when it deals with systems for "rare diseases", "retinitis pigmentosa" and "pupillometry". Among all the found articles, the seven resumed below were chosen based on regency and variety, so as to have different views of general approaches when ML interfaces with eye diseases. Brancati et al. apply ML supervised techniques for detecting pigment signs on fundus images acquired with a digital retinal camera to study patients affected by RP. Gao et al. apply the ML random forest algorithm on optical coherence tomography (OCT) images to support the diagnosis of choroideremia by detecting intact choriocapillaris. Four more articles apply similar supervised ML algorithms to common eye diseases such as age-related macular degenerations diabetic retinopathy and glaucoma . Gargeya et al. bring a different approach to support the diagnosis of diabetic retinopathy using deep learning. The results from the studies just cited are summarized

PROPOSED SYSTEM :

The non-invasiveness is granted by adopting the proposed pupillometric method, which requires no specific patient preparations with drugs or collyriums. If com- pared with other standard diagnostic techniques, particularly, electrorheological test, in this case no electrodes need to be placed on the patient skin: this is particularly convenient when dealing with pediatric patients. Particularly, in younger children the electrophysiological testing are usually per- formed in sedation, thus requiring a more complex clinical setting (i.e. availability of operating theater together with anesthesiologist). Chromatic pupillometry has been proven to be effective in diagnosis of RP.

SYSTEM STUDY :

FEASIBILITY STUDY :

The feasibility of the project is analyzed in this phase and business proposal is put forth with a very general plan for the project and some cost estimates. During system analysis the feasibility study of the proposed system is to be carried out. This is to ensure that the proposed system is not a burden to the company. For feasibility analysis, some understanding of the major requirements for the system is essential.

- ECONOMICAL FEASIBILITY
- TECHNICAL FEASIBILITY
- SOCIAL FEASIBILITY

ECONOMICAL FEASIBILITY :

This study is carried out to check the economic impact that the system will have on the organization. The amount of fund that the company can pour into the research and development of the system is limited. The expenditures must be justified. Thus the developed system as well within the budget and this was achieved because most of the technologies used are freely available. Only the customized products had to be purchased.

TECHNICAL FEASIBILITY :

This study is carried out to check the technical feasibility, that is, the technical requirements of the system. Any system developed must not have a high demand on the available technical resources. This will lead to high demands on the available technical resources. This will lead to high demands being placed on the client. The developed system must have a modest requirement, as only minimal or null changes are required for implementing this system.

SOCIAL FEASIBILITY :

The aspect of study is to check the level of acceptance of the system by the user. This includes the process of training the user to use the system efficiently. The user must not feel threatened by the system, instead must accept it as a necessity. The level of acceptance by the users solely depends on the methods that are employed to educate the user about the system and to make him familiar with it. His level of confidence must be raised so that he is also able to make some constructive criticism, which is welcomed, as he is the final user of the system.

SYSTEM DESIGN :

SYSTEM ARCHITECTURE :

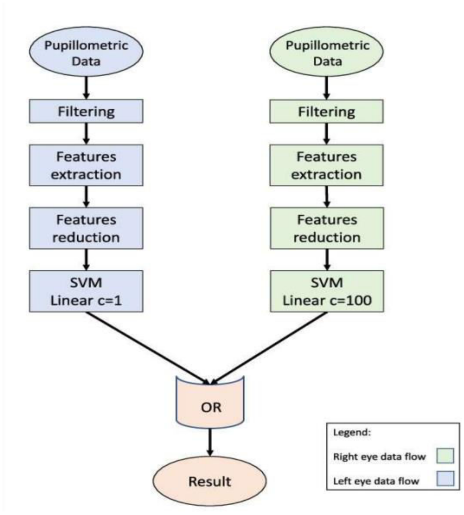


Fig1: system architecture

UML DIAGRAMS :

UML stands for Unified Modeling Language. UML is a standardized generalpurpose modeling language in the field of object-oriented software engineering. The standard is managed, and was created by, the Object Management Group. The goal is for UML to become a common language for creating models of object oriented computer software. In its current form UML is comprised of two major components: a Meta-model and a notation. In the future, some form of method or process may also be added to; or associated with, UML.

USE CASE DIAGRAM:

A use case diagram in the Unified Modeling Language (UML) is a type of behavioral diagram defined by and created from a Use-case analysis. Its purpose is to present a graphical overview of the functionality provided by a system in terms of actors, their goals (represented as use cases), and any dependencies between those use cases. The main purpose of a use case diagram is to show what system functions are performed for which actor. Roles of the actors in the system can be depicted.

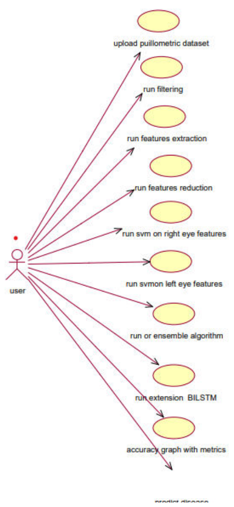


Fig2: use case

CLASS DIAGRAM:

In software engineering, a class diagram in the Unified Modeling Language (UML) is a type of static structure diagram that describes the structure of a system by showing the system's classes, their attributes, operations (or methods), and the relationships among the classes. It explains which class contains information.

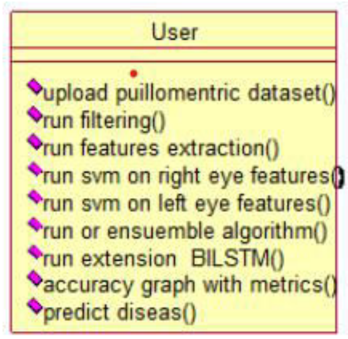


Fig3: class diagram

SEQUENCE DIAGRAM:

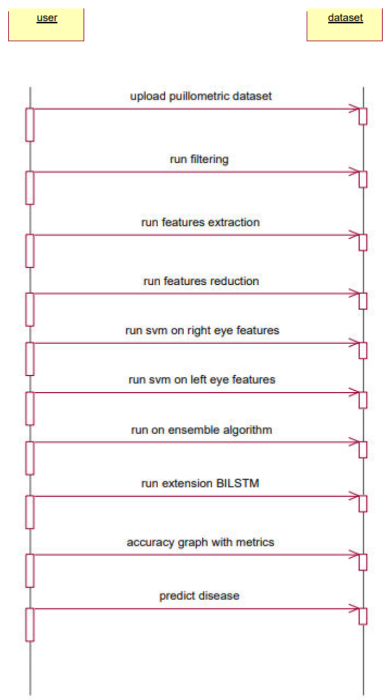


Fig4: sequence diagram

COLLABRATION DIAGRAM:

Activity diagrams are graphical representations of workflows of stepwise activities and actions with support for choice, iteration and concurrency. In the Unified Modeling Language, activity diagrams can be used to describe the business and operational step-by-step workflows of components in a system. An activity diagram shows the overall flow of control.

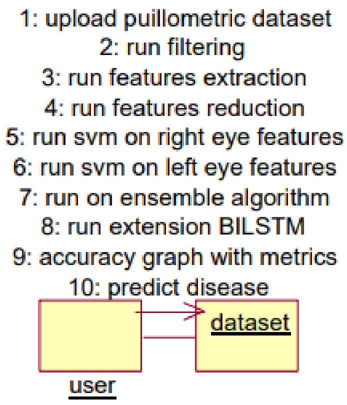


Fig5: collaboration diagram

IMPLEMENTATION:

MODULES:

UPLOAD PUILLOMETERIC DATASET

RUN FEATURES EXTRACTION

RUN FEATURES EXCATION

RUN SVM ON RIGHT EYE FEATURES

RUN SVM ON LEFT EYE FEATURES

RUN ON ENSEMBLE ALGORITHM

RUN EXTENDSION BILSM ACCRACY GRAPH WITH METRICS PREDICT DISEASE

SYSTEM TEST :

The purpose of testing is to discover errors. Testing is the process of trying to discover every conceivable fault or weakness in a work product. It provides a way to check the functionality of components, sub assemblies, assemblies and/or a finished product It is the process of exercising software with the intent of ensuring that the Software system meets its requirements and user expectations and does not fail in an unacceptable manner. There are various types of test. Each test type addresses a specific testing requirement

TYPES OF TESTS :

UNIT TESTING :

Unit testing involves the design of test cases that validate that the internal program logic is functioning properly, and that program inputs produce valid outputs. All decision branches and internal code flow should be validated. It is the testing of individual software units of the application .it is done after the completion of an individual unit before integration. This is a structural testing, that relies on knowledge of its construction and is invasive. Unit tests perform basic tests at component level and test a specific business process, application, and/or system configuration. Unit tests ensure that each unique path of a business process performs accurately to the documented specifications and contains clearly defined inputs and expected results.

INTEGRATION TESTING :

Integration tests are designed to test integrated software components to determine if they actually run as one program. Testing is event driven and is more concerned with the basic outcome of screens or fields. Integration tests demonstrate that although the components were individually satisfaction, as shown by successfully unit testing, the combination of components is correct and consistent. Integration testing is specifically aimed at exposing the problems that arise from the combination of components.

FUNCTIONAL TESTING :

Functional tests provide systematic demonstrations that functions tested are available as specified by the business and technical requirements, system documentation, and user manuals.

Valid Input :

Identified classes of valid input must be accepted.

Invalid Input :

Identified classes of invalid input must be rejected.

Functions :

Identified functions must be exercised.

Output :

Identified classes of application outputs must be exercised.

Systems/Procedures :

Interfacing systems or procedures must be invoked. Organization and preparation of functional tests is focused on requirements, key functions, or special test cases. In addition, systematic coverage pertaining to identify Business process flows; data fields, predefined processes, and successive processes must be considered for testing. Before functional testing is complete, additional tests are identified and the effective value of current tests is determined.

System Test:

System testing ensures that the entire integrated software system meets requirements. It tests a configuration to ensure known and predictable results. An example of system testing is the configuration oriented system integration test. System testing is based on process descriptions and flows, emphasizing pre-driven process links and integration points.

White Box Testing:

White Box Testing is a testing in which in which the software tester has knowledge of the inner workings, structure and language of the software, or at least its purpose. It is purpose. It is used to test areas that cannot be reached from a black box level.

Black Box Testing:

Black Box Testing is testing the software without any knowledge of the inner workings, structure or language of the module being tested. Black box tests, as most other kinds of tests, must be written from a definitive source document, such as specification or requirements document, such as specification or requirements document. It is a testing in which the software under test is treated, as a black box .you cannot "see" into it. The test provides inputs and responds to outputs without considering how the software works

Unit Testing:

Unit testing is usually conducted as part of a combined code and unit test phase of the software lifecycle, although it is not uncommon for coding and unit testing to be conducted as two distinct phases.

Test strategy and approach:

Field testing will be performed manually and functional tests will be written in detail. Test objectives

• All field entries must work properly.

• Pages must be activated from the identified link.

• The entry screen, messages and responses must not be delayed. Features to be tested

• Verify that the entries are of the correct format

• No duplicate entries should be allowed

• All links should take the user to the correct page

Integration Testing :

Software integration testing is the incremental integration testing of two or more integrated software components on a single platform to produce failures caused by interface defects. The task of the integration test is to check that components or software applications, e.g. components in a software system or – one step up – software applications at the company level – interact without error.

Acceptance Testing :

User Acceptance Testing is a critical phase of any project and requires significant participation by the end user. It also ensures that the system meets the functional requirements.

RESULTS:

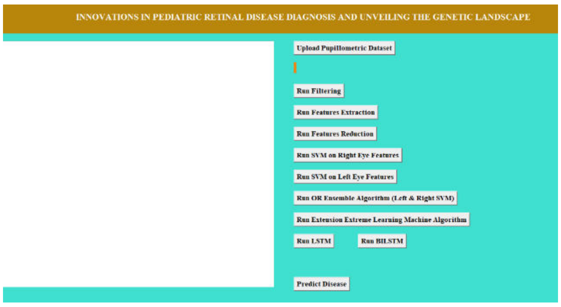


fig6: To run project double click on 'run.bat' file to get below screen

Fig7: Now click on 'Run Filtering' button to perform filtering on dataset to ignore raw data

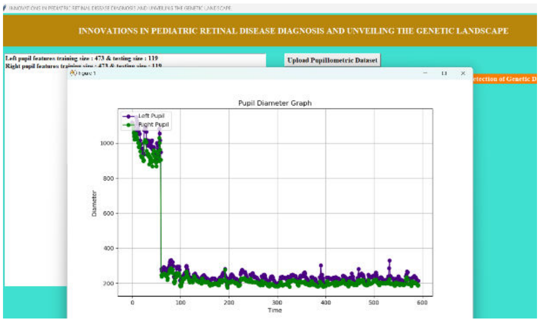


Fig8: In above graph x-axis represents time of pupil capture and y-axis represents diameter of pupils. Blue line represents left pupil and green line represents right pupil. Close above graph to get below screen

In above screen application using 473 records for training and 119 records for testing from total 593 records. Now click on 'Run SVM on Right Eye Features' to run SVM classifier

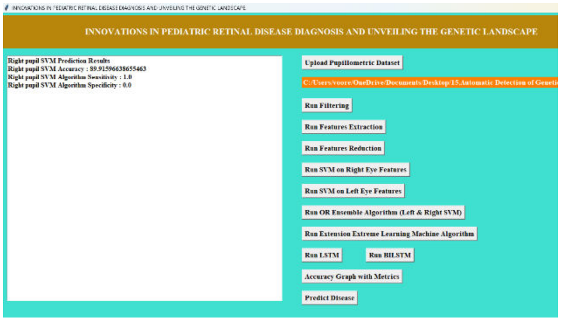


fig9: In above screen with Ensemble OR SVM we got 86% accuracy and now click on 'Run Extension BILSTM' button to run BILSTM algorithm and get below output

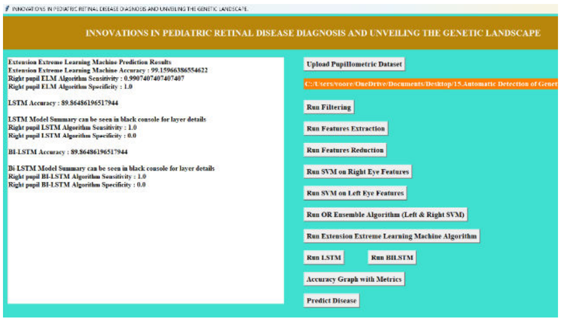


fig10: In above screen with extension 'BILSTM' we got 89% accuracy and now click on 'Accuracy Graph with Metrics' to get below accuracy graph

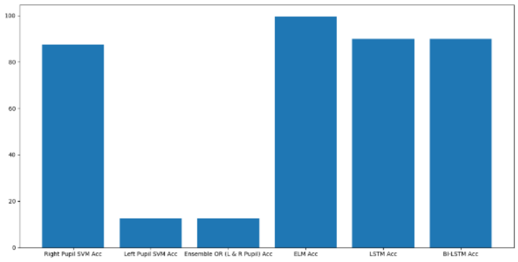
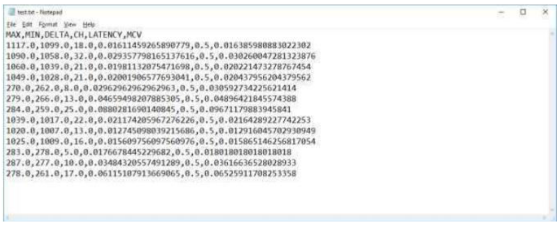


fig11: In above graph x-axis represents algorithm name and y-axis represents accuracy and in all algorithms extension BILSTM got high accuracy and now click on 'Predict Disease' button to upload test data and predict disease. In below test data we can see only pupil values are there but not disease information and classifier will predict disease information after applying classifier on it.


test.txt - Notepad

File Edit Format View Help

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MAX,MIN,DELTA,CH,LATENCY,MCV
1117.0,1099.0,18.0,0.016114592658907 79,0.5,0.01638598088 3022302
1090.0,1058.0,32.0,0.029357798165137616,0.5,0.030260047281323876
1060.0,1039.0,21.0,0.019811320754716 98,0.5,0.020221473278767454
1049.0,1028.0,21.0,0.020019065776930 41,0.5,0.020437956204379562
270.0,262.0,8.0,0.02962962962962963,0.5,0.030592734225621414
279.0,266.0,13.0,0.04659498207885305,0.5,0.04896421845574388
284.0,259.0,25.0,0.0880281690140845,0.5,0.09671179883945841
1039.0,1017.0,22.0,0.021174205967276226,0.5,0.021642892277 42253
1020.0,1007.0,13.0,0.012745098039215686,0.5,0.012916045702930949
1025.0,1009.0,16.0,0.015609756097560976,0.5,0.015865146256817054
283.0,278.0,5.0,0.0176678445229682,0.5,0.018018018018018018
287.0,277.0,10.0,0.03484320557491289,0.5,0.03616636528028933
278.0,261.0,17.0,0.06115107913669065,0.5,0.06525911708253358
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fig12: In above test data 'test.txt' we have only features values and after uploading classifier will predict disease.

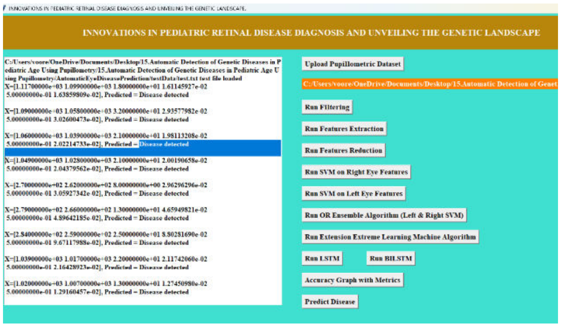

fig13: In above screen for each test record classifier displaying predicted result as 'disease detected' or 'no disease detected'. In above screen in square bracket we can see TEST values and after square bracket we can see predicted result as pupillometri disease detected or not. Here we are extracting data from binocular device data and we are splitting train and test data as random so accuracy may vary for each run based on collected data from binocular device data.

CONCLUSION:

This paper describes a new approach for supporting clinical decision for diagnosis of retinitis pigmentosa starting from analysis of pupil response to chromatic light stimuli in pedi- atric patients. The system was developed to clean artefacts, extract features and help the diagnosis of RP using a ML approach based on an ensemble model of two fine-tuned SVMs. Performances were evaluated with a leave-one-out cross-validation, also used to identify the best combination of internal parameters of the SVM, separately for both the left and right eyes. The class assigned to each eye were combined in the end with an OR-like approach so as to maximize the overall sensitivity of the CDSS; the ensemble system achieved 99.59% accuracy.The small amount of data available for this work, calls for further tests with a larger data pool for validating the performance of the system. Future scope includes testing the same approach with different devices .

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