FUNAGES: AN EXPERT SYSTEM FOR FUNDUS FLUORESCEIN ANGIOGRAPHY

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ABSTRACT

FUNAGES is an expert system that deals with the interpretation of fundus fluorescein angiography. Fluorescein angiography is an extremely valuable clinical test that provides information about the circulatory system of the ocular fundus (the back of the eye) not attainable with a routine examination. The different, in place and time, appearance of fluorescein and the classification of the fundus diseases render angiography a dynamic, cinematographic and deductive diagnostic method. Therefore, the knowledge for interpreting fundus fluorescein angiograms allows an ophthalmologist specialized in ocular fundus diseases to follow a systematic, orderly and logical line of reasoning that leads to a proper diagnosis. FUNAGES was developed to simulate the above logical reasoning, in order to facilitate the inexperienced ophthalmologists in the interpretation of the angiograms. The system achieved its purposes in an adequate way via a graphical user interface and a thorough knowledge base.

Keywords: Expert Systems, Artificial Intelligence in Medicine

INTRODUCTION

Artificial Intelligence in Medicine (AIM) as a field emerged in the early 1970's in response to several simultaneous needs, opportunities, and interests. An increased demand for high-quality medical services coupled with the explosive growth of medical knowledge has led to the suggestion that computer programs could be used to assist physicians and other health care providers in discharging their clinical roles in diagnosis, therapy and prognosis. At the same time, computer science techniques, especially those of the artificial intelligence field, began to reach a maturity with which they could be applied to representing and reasoning about complex, "real world" problems like those arising in medicine. Investigators trained on both the computational and the medical side of these concerns began to develop mutual interests and approaches, and to form coherent collaborative research [1].

One of the first uses of artificial intelligence (AI) on a practical level was the coupling of expert medical knowledge with computer-based technology. As early as the 1960s, computer scientists and physicians recognized the possibility that computers, with their speed and ability to perform complex arithmetic operations, could assist doctors in the diagnosis and treatment of disease [2]

Several prototype computer programs tackle difficult clinical problems in a manner similar to that of an expert physician. The most prominent of them are: INTERNIST [3], a diagnostic aid that combines a large database of disease/manifestation associations with techniques for problem formulation; EXPERT [4] and CASNET/Glaucoma [5] which use physiological models for the diagnosis and treatment of eye disease; MYCIN [6], a rule-based program for diagnosis and therapy selection for infectious diseases; the Digitalis Therapy Advisor [7], which aids the physician in prescribing the right dose of the drug digitalis and also explains its actions; and ABEL [8], a program that uses multi-level pathophysiologic models for diagnosis of acid-base and electrolyte disorders.

A very popular expert system for ophthalmology is VIBES (Visual Impairments and Blindness Expert System) [9]. VIBES consists of categories and was developed to help answer questions and give advice. Each category contains a discussion of many tasks and cross-references to alternative techniques, which can be used by people who are visually impaired or blind. It also cross-references to any products like Audio, CCTVs, Electronic Media, Integrated Software, Newsletters, Paper Media, Printers or services such as Conferences and Readers, which are available to help accomplish each task.

This paper introduces FUNAGES [10], an expert system that deals with the interpretation of fundus fluorescein angiography. Fluorescein angiography is a sophisticated widely used diagnostic test, which allows the clinician and researcher to understand underlying histopathologic changes of fundus diseases in vivo [11], [12]. Quite a few pattern recognition systems try to identify regions of interest in such angiographies [13], [14], [15], [16]. However, to the best of our knowledge, there is no expert system in the literature for aiding the interpretation of fundus fluorescein angiograms.

The profound impact of fluorescein angiography in ophthalmology necessitates a simple and logical means of interpreting angiograms. The primary purpose of FUNAGES, therefore is to present a simplified method of interpreting fluorescein angiograms in order to facilitate the novice ophthalmologists to follow a systematic, orderly and logical line of reasoning that leads to a proper diagnosis. Furthermore, FUNAGES can also be used as a teaching aid for the fundus fluorescein angiography diagnostic methodology, since novice ophthalmologists can harmlessly experiment with "what-if" scenarios, using the backtracking ability of the system's question answering interface.

It must be noticed here that the performance of FUNAGES compared to an expert ophthalmologist can be no worse, since FUNAGES does not automatically interpret fundus fluorescein angiograms but merely helps an ophthalmologist to follow a specific diagnostic methodology. Therefore, the quality of the final diagnosis still depends on the ophthalmologist's judgement at each step of the diagnostic procedure.

The rest of the paper is organised into three sections. The next (second) section introduces fundus fluorescein angiography and discusses its features that allow the modeling of its interpretation in an expert system. The third section presents the FUNAGES system, along with its architecture, operation, and development process. Finally, the fourth section concludes with a brief discussion on FUNAGES’s successes, recommendations for future work and a reference on current work that will take the system further.

FLUORESCEIN ANGIOGRAPHY

Fluorescein angiography is an extremely valuable test that provides clinical information about the circulatory system of the ocular fundus (the back of the eye) not attainable with a routine examination. The test is performed by injecting a special dye called sodium fluorescein into a vein in the arm. In few seconds, the dye travels to the blood vessels inside the eye. A camera equipped with special filters that highlight the dye is used to photograph the path of the fluorescein as it circulates though the eye. In many cases, these photos are taken with a digital camera system, allowing the physician to interpret the results immediately.

The technique is based on the phenomenon of fluorescence, which entails a shift from a shorter wavelength (which corresponds to higher energy) in the excitation radiation to a longer wavelength (which corresponds to lower energy) in the emitted light.

Fluorescein angiography constitutes a major advance in medical ophthalmology. It contributes greatly to the diagnosis of fundus lesions. Combined with information derived from other clinical examination techniques and histological specimens, the pathophysiologic information obtained by Fluorescein angiography has allowed the clinician and researcher to understand underlying histopathologic changes of fundus diseases in vivo [11].

Two distinct features of fundus facilitate the whole procedure: (1) The histology of fundus with its stratification along with its cellular and visual barriers; and (2) the sequence filling of its dual circulations, retinal and choroidal, which can be differentiated from Fluorescein angiography.

The different, in place and time, appearance of fluorescein renders angiography a dynamic, cinematographic diagnostic method [12]. Additionally, the various changes in the fluorescein angiogram can be categorized. The categories can then broken down into subclasses and finally into etiologic factors. The classification can be logical and complete.

The simplicity of this classification compared to the complexity of the information given by a simple observation of the fundus with polychromatic white light, render angiography a deductive diagnostic method. Consequently, fundus fluorescein angiography can be utilized as a valuable research tool and a guide for evaluating fundus diseases.

FUNAGES [10] is a computerised system that was developed to aid in the visualisation, perception, and appreciation of fundus fluorescein angiography interpretation process in order to facilitate the novice ophthalmologists to follow a systematic, orderly and logical line of reasoning that leads to a proper diagnosis.

THE FUNAGES SYSTEM

In this section, we present the FUNAGES system, i.e. its architecture and operation, as well as its development process. FUNAGES [10] is an expert system that aims to aid non-specialised ophthalmologists to reach diagnosis via the interpretation of fundus fluorescein angiograms. The system interacts with the user obtaining just the necessary information regarding the state of the patient’s fundus during the different phases of the angiography. Accurate diagnosis is achieved by the use of appropriately encoded medical knowledge and an efficient inference engine. The knowledge base of the system contains highly specialised knowledge on the problem area as provided by the expert, which has been engineered in a structured manner.

The development of the FUNAGES system consisted of 5 stages:

- Knowledge Acquisition
- Knowledge Representation
- Development of the Expert System prototype
- Development of the User-Interface
- System Integration

Knowledge Acquisition

This stage, involved interviews held with the expert, an ophthalmologist specialized in fundus fluorescein angiography, where several aspects of the problem were discussed. Furthermore, a broad bibliographical material on fundus fluorescein angiography was covered by the knowledge engineer, in order a) to acquire background knowledge on the subject, so that she could go along with the ophthalmologist, and b) to obliterate the subjectivity of the single expert.

During the early stages of the knowledge acquisition material of a general nature was covered. The objective was to uncover key concepts and general problem-solving methods used by the expert. Later sessions took advantage of information gained from questionnaires, filled by the expert. There was one questionnaire per disease. Figure 1 is an example of such a questionnaire.

Knowledge Representation

Following the knowledge acquisition stage, the best approach for representing the expert's knowledge and problem-solving strategy in the system was decided during the knowledge modelling and representation stages. The various changes in the fluorescein angiogram can be categorized. The categories can then be broken down into subclasses and finally into etiologic factors. The classification can be logical and complete. Therefore, the system's requirements were suitable for semi-structured knowledge representation methods such as decision trees and tables [11]. A sample fragment of the decision tree is shown in Figure 2.

The tree offers a simple and logical line of reasoning for the interpretation of the fluorescein angiogram. The first step in this incremental decision making process is to recognise areas of abnormal fluorescence and determine whether they are hypofluorescent or hyperfluorescent (Node 1). Hypofluorescence is the reduction or absence of normal fluorescence, whereas hyperfluorescence is excessive fluorescence.

After this initial differentiation decision, similar decision nodes follow in order to arrive at a proper diagnosis. These decisions depend upon the anatomic location of various abnormalities, quality and quantity of the abnormal fluorescence, and other unique characteristics as indicated in the decision tree (Figure 2). For example, if an area of hypofluorescence is recognised, it is necessary to refer to the ophthalmoscopic photograph to determine the cause. If there is ophthalmoscopically visible material that corresponds to the area of hypofluorescence, then it is inferred that this is blocked fluorescence, whilst the absence of a material indicates a vascular filling defect (Node 2).

After the cause of abnormality is determined, the next step is to determine its anatomic location or to determine which of the two fundus circulations is involved. In the case of blocked fluorescence, the blocking material affects the retinal and choroidal circulations, if it is located on or in front of the retina. The material blocks only the choroidal circulation, if it is located beneath the retinal circulation and in front of the choroid (Node 3).

Blocked retinal vascular hypofluorescence is caused by anything that reduces media clarity. Any opacification in front of the retinal vessels involving either the anterior chamber, vitreous, or the most anterior portion of the retina or disc will reduce fluorescence (Node 4). The further the opacification is in front of the fundus, the less it will block fluorescence and the more it will affect the overall quality of the photographs. The closer the material is to the fundus, the more it will block causing hypofluorescent images on the angiogram.

The exact final diagnosis (Nodes 5, 6, 7) is based on the unique characteristics of every abnormality. The characteristics are related to:

- The colour of the defect
- The type of the fluorescence during the four phases of the angiography:
  - Phase 1: Early choroidal filling
  - Phase 2: Retinal arterial filling and increased choroidal filling
  - Phase 3: Full retinal arteriovenous and choroidal filling
  - Phase 4: Reduced retinal and choroidal fluorescence, late disc staining and visible sclera
- The morphology of the defect regarding the contour, the frequency, the texture and the profile

In some cases additional clinical information is required for achieving a proper unique diagnosis.

System Design and Architecture

During the design stage [17], the architecture of the system was developed taking into account the constraints imposed by the user requirements and the available technology. The system architecture comprises the function units of the system accompanied by their operations and dependencies (Figure 3).

There are two major components: the expert system and the user interface. The CLIPS expert system programming language [18] was chosen to represent and reason with the system's knowledge in a manner that is similar to the approach taken by the human expert. A user-friendly interface was built using the visual application development environment of DELPHI [19] language. CLIPS and DELPHI are in continuous interaction via the dynamic link library `Clips.dll`. This library component contains all the functions necessary to interpret the production rule language of CLIPS, but lacks a user interface. The DELPHI component is the main program whilst the expert system is evoked from DELPHI on demand, by calling functions of the dynamic linked library. Inversely, CLIPS returns values to the main program by using indirect disk files. For this reason, two text files were created: `NextFormFile` and `DiagnosisFile.` The former is used for storing the name of the next form, which will be read by DELPHI and appeared to the user and the latter for storing the code number of the final diagnosis.

As shown in Figure 4, the user inputs data through the DELPHI component (user interface), which consequently calls the CLIPS component (knowledge base), feeding the user input data. The knowledge base is being consulted and decisions are made concerning which is the next input form to display to the user. The user goes on with answering questions and the procedure is repeated until the CLIPS' inference engine comes to a final diagnosis, which is displayed by the DELPHI component to the user.

Development of the Expert System Prototype

CLIPS language was chosen as the software tool for knowledge representation and reasoning. Knowledge is contained in `KnowledgeBase` and is organised in production rules. A production rule is a collection of conditions and the actions to be taken if the conditions are met. Rules execute (fire) based on the existence or non-existence of facts or instances of user-defined classes. CLIPS provides the mechanism (the inference engine) which attempts to match the rules against the current state of the system, which is represented by the fact-list and instance-list and to apply the corresponding actions.

The initialisation rule in FUNAGES' knowledge base performs the following actions:

1. Initialises the global variable that contains the code number of the diagnosis.
2. Updates the fact-list with the fact of the existence of abnormal fluorescence.
3. Sets the conflict strategy to depth.
4. Sets fact duplication option to FALSE, forbidding the reactivation of a rule.

Another rule cluster is responsible for the traversing of the decision tree. At each node of the tree, there are as many rules as the number of successor nodes. The current set of answers that the user supplied determines which rule's condition is satisfied. The actions of the fired rule update the file `NextFormFile` with the name of the form that contains the next set of questions to be asked to the user. These questions determine the path that will be followed through the decision tree.

There is another set of rules that are used when the position and the characteristics of the abnormality concur for more than one disease. The actions of these rules ask for clinical information from the user, if available. The user is prompted with a list of relevant only pieces of clinical information.

Finally, there are diagnostic rules whose actions update the fact-list for the final diagnosis, output the code number of the diagnosis to the file `DiagnosisFile`, which will be presented by the DELPHI component to the user.

Additionally there are rules that are used for fact retraction from the fact-list. These rules fire when the user backtracks to previous forms in order to change the answers to some system's prior questions.

The CLIPS component executed following the steps:

1. Cleaning the environment
2. Loading the knowledge base
3. Inserting the initial facts in the fact-list
4. Running the program

The above steps are executed by evoking appropriate function calls of the CLIPS dynamic link library from the DELPHI component of the application.

Development of the User-interface and System Integration

In order to build a user-friendly, intelligent environment we employed to different programming technologies, such as expert systems and visual programming, brought by CLIPS and DELPHI respectively.

DELPHI was used to implement forms containing questions necessary for determining abnormalities. The user is requested to answer questions by choosing answers from given lists, assisting FUNAGES to reach a valid diagnosis.

After the initial launching of FUNAGES, the user is prompt to characterize the kind of the abnormal fluorescence (Figure 5). After the user's answer, the following actions take place:

- Storing the user's answer in the DELPHI environment
- Initializing CLIPS using the dynamic link library)
- Loading the knowledge base in CLIPS
- Error checking for loading
- Inserting the user's answer in the CLIPS environment (as a fact in the fact-list)
- Executing CLIPS application

If the knowledge base is loaded without errors, `NextFormFile` is updated with the name of the next form over which the DELPHI component prompts the user with the subsequent questions. Contrarily, in case of an error, the user is informed by a relative message. Finally, the user is warned by a beeping sound when continuity is requested without any selected answer.

Subsequently, several forms appear in order to seek e.g. the cause and the exact location of the abnormality, the affected circulations, etc. These forms appear together in the same window for better oversight (Figure 6).

During the next diagnosis step, FUNAGES presents a form containing questions about abnormality's particular characteristics, as illustrated in Figure 7. The system receives the user's answers and adds them, as new facts, in the fact-list. The CLIPS component is evoked once more.

When a final diagnosis can be directly reached, FUNAGES informs user with a corresponding form. On the contrary, if the evidence gathered by the system leads to more than one diagnosis, the user is requested to give additional clinical information, if available, choosing from a list that contains only the relevant clinical information of the potential diseases. An example of this form is shown in Figure 8.

When a final diagnosis is reached, the last cycle of the CLIPS component is executed updating the file `Diagnosis` with the code number of the diagnosis. Subsequently, the DELPHI component displays to the user an appropriate form that contains the name of the diagnosis and some sample angiograms of it. (Figure 9).

If no diagnosis is accomplished the user is informed by a corresponding message.

CONCLUSIONS – FUTURE WORK

The knowledge for interpreting fundus fluorescein angiograms allows an ophthalmologist specialized in ocular fundus diseases to follow a systematic, orderly and logical line of reasoning that leads to a proper diagnosis. FUNAGES was developed to simulate the above logical reasoning, in order to facilitate the novice ophthalmologists in the interpretation of the angiograms.

The system's reliability, efficiency and maintenance are due to the careful design, the modular development of the rule-base, the early development and evaluation of the system prototypes and the validity tests performed on the final prototype. Actually, two prototypes were developed; the first was developed in CLIPS for validating the acquired knowledge, while the second one was developed in DELPHI for evaluating the user-interface.

The system's diagnostic efficiency is based on the graphical user interface that facilitates the user through a cooperative style of interaction. It uses an adequate number of forms so that an analytical, systematic reasoning can be followed by the physician without making him/her tired or bored. The forms are presented so that good oversight is obtained without increasing its complexity in appearance.

The FUNAGES system attempts to improve the effectiveness of diagnosis (accuracy, timeliness, quality) that is performed by a human ophthalmologist, rather than improve his/her efficiency of making decisions. Therefore, the diagnoses made by FUNAGES are at least as good as those of a human are, since at each step it is the human that judges the fundus fluorescein angiograms and answers the questions.

The system's knowledge base has been evaluated positively by an ophthalmologist that is an expert in interpreting fundus fluorescein angiograms. The same expert, along with his apprentice ophthalmologists, evaluated the system's functionality. It was due to this evaluation that the backtracking feature was introduced to the user interface, so that user's at any step can revise their earlier decisions. Actually, this feature of the system has been used by the evaluators to be trained mode deeply in the diagnostic process by experimenting with "what-if" scenarios.

Since FUNAGES’s knowledge and control are separated, the tasks of modifying and maintaining the system are easy. Adding new knowledge or modifying existing knowledge requires minor changes to the knowledge base. This is made possible by clustering the rules into independent sets, so that each rule cluster is used only on an as-needed basis. Therefore, the addition or deletion of a rule affects possibly only its rule cluster. Changes to the control knowledge are achieved by adjusting the inference engine’s strategy.

FUNAGES can be extended for covering a greater range of ocular diseases by expanding its knowledge base with new rules. Here, we must notice that the ability of multiple fundus diseases diagnosis was not considered, since abnormalities can be handled independently from each other. The latter was realized by the knowledge acquisition phase.

The system’s diagnostic ability can be improved by taking into account the results of other clinical and paraclinical tests as for example visual acuity, visual field deficits electrophysiology and ultrasound finding. Of course, the full automatization of the interpretation of the angiograms using image recognition approaches is our long-term goal.

Finally, we are currently working on improving the user-interface so that the physician can answer questions in a more flexible way, i.e. instead of answering a yes/no question he/she could have a scaled range of possible answers between the two extremes. Of course, this requires that the answers should be combined with the knowledge base using fuzzy logic. In this way, more accurate reasoning and results will be obtained. This would require, of course, certain changes in the user-interface to account for fuzzy-linguistic user answers.

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Diagnosis	**Nerve fibre edema**

1. Color of the defect

Unsaturated-Fundus	✔
Grey –White	✔
Yellow – Gold	
Red	
Orange	
Brown-Black	

2. Morphology of the defect

Well Defined		Simple	
Ill Defined	✔	Multiple	✔

Smooth		Embossed	✔
Rough	✔	Engraved	

3. Fluorescence during angiography four phases

Phase	Early choroidal filling	Retinal arterial filling Increased choroidal filling	Full retinal arteriovenous & choroidal filling	Reduced retinal & choroidal fluorescence Late staining of disc & visible sclera
Hypo	✔	✔	✔	✔
Hyper			✔	✔

4. Clinical Information

Figure 1: Sample of questionnaire

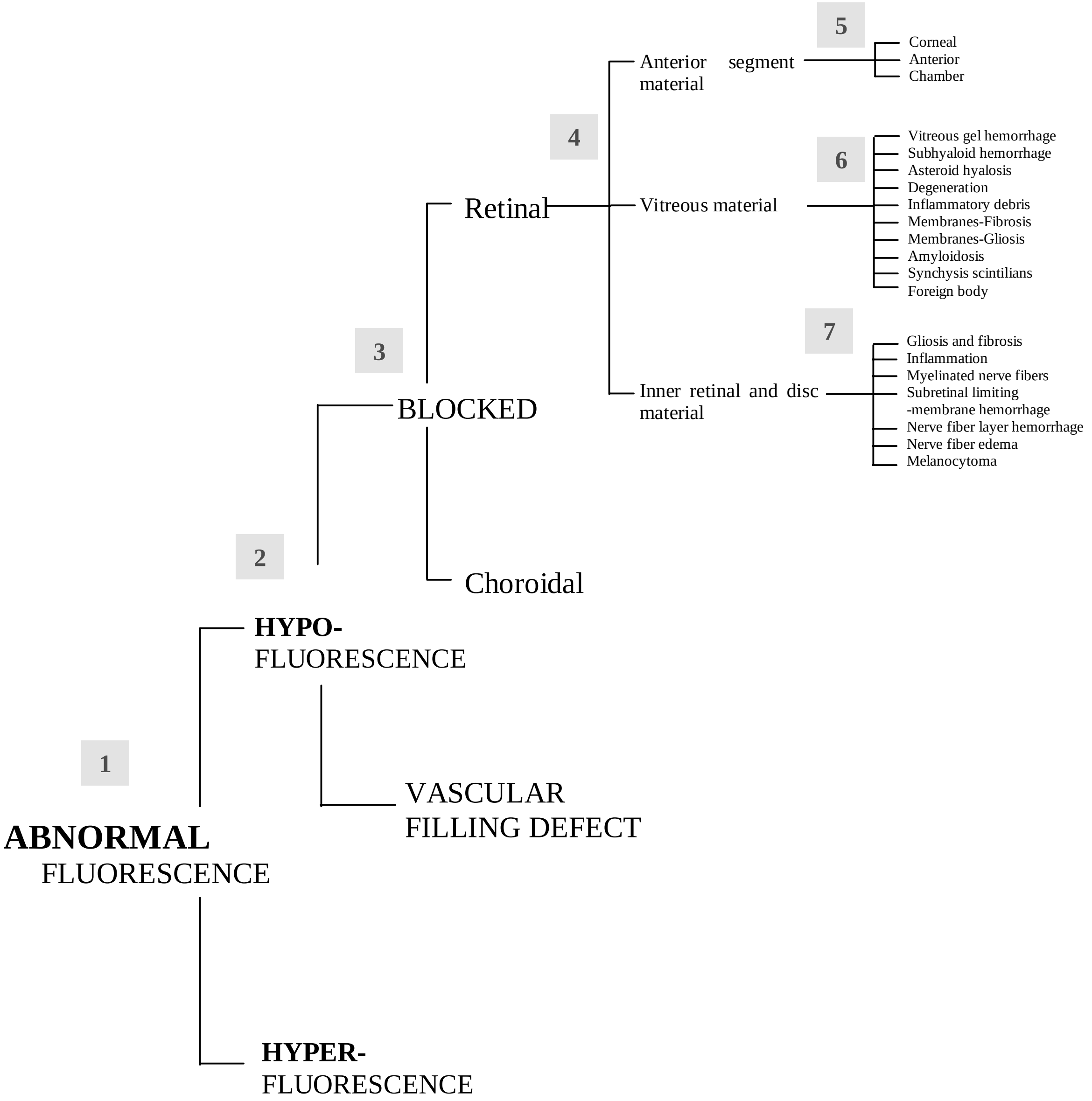

Figure 2: A sample fragment of the decision tree

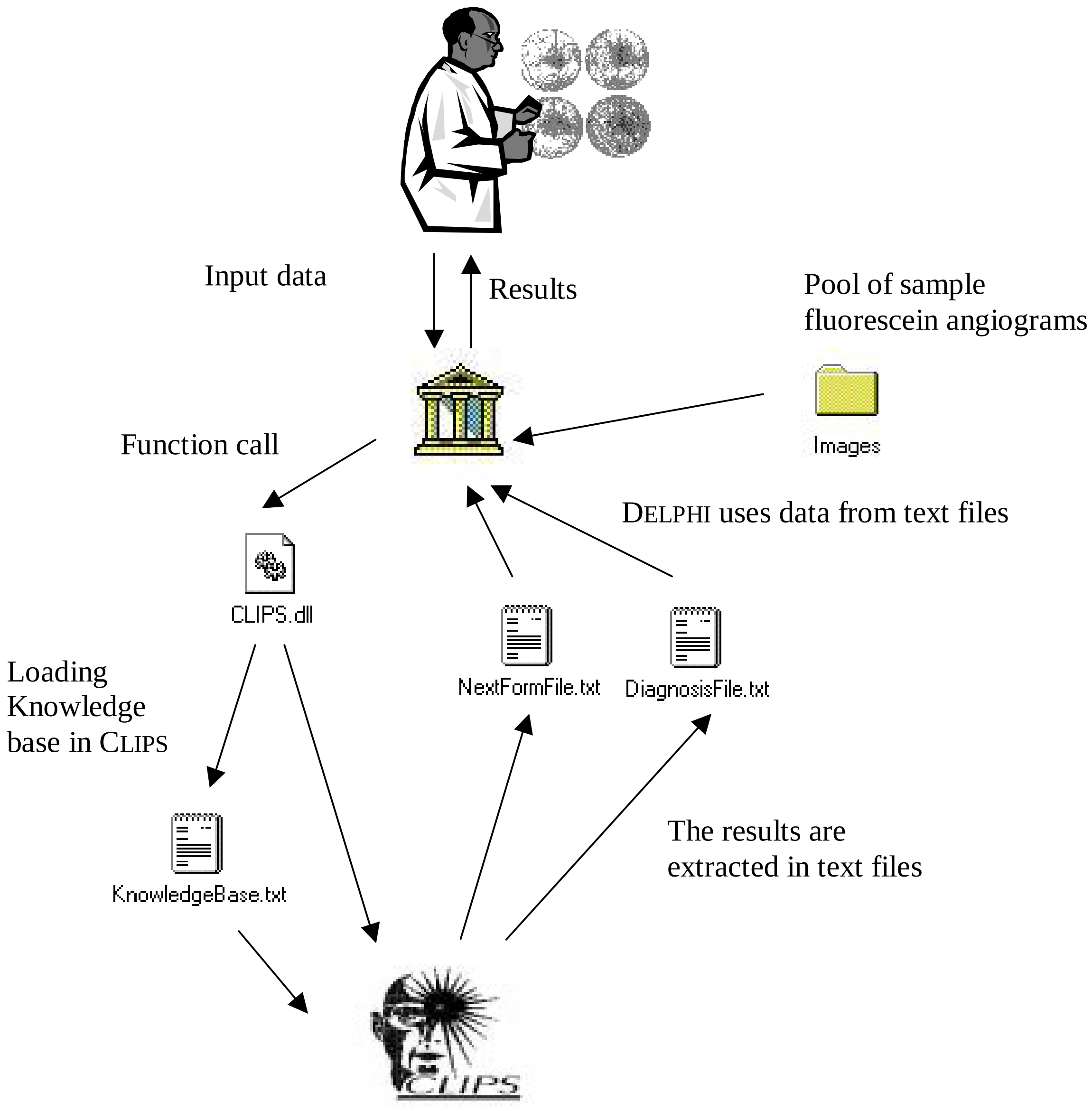

Figure 3: System Architecture

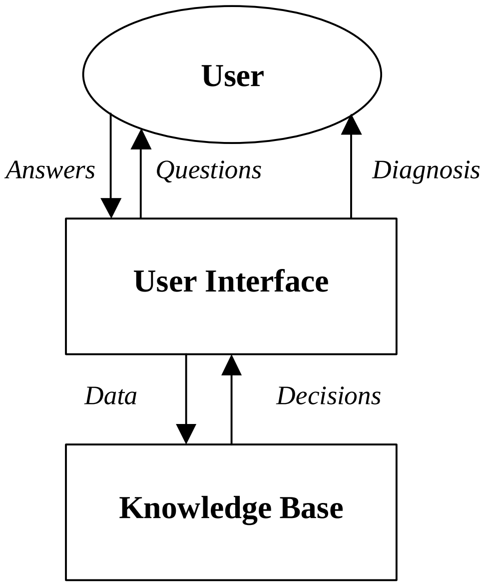

Figure 4: System Operation

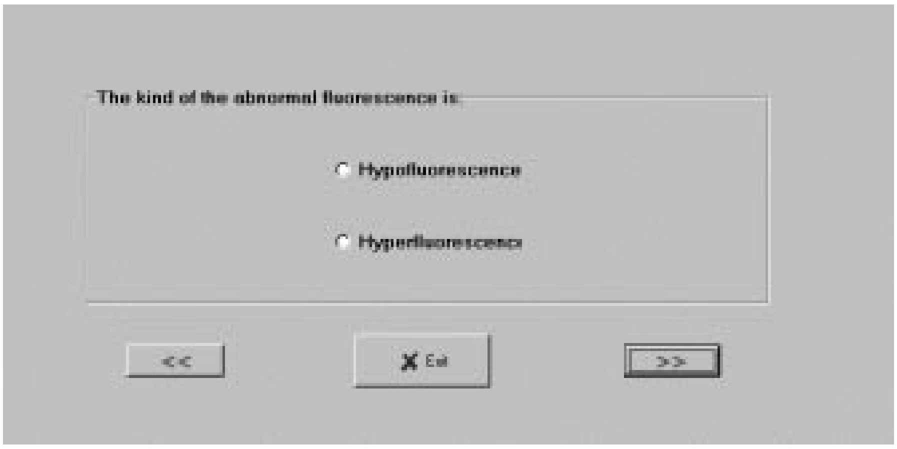

Figure 5: Abnormal fluorescence form

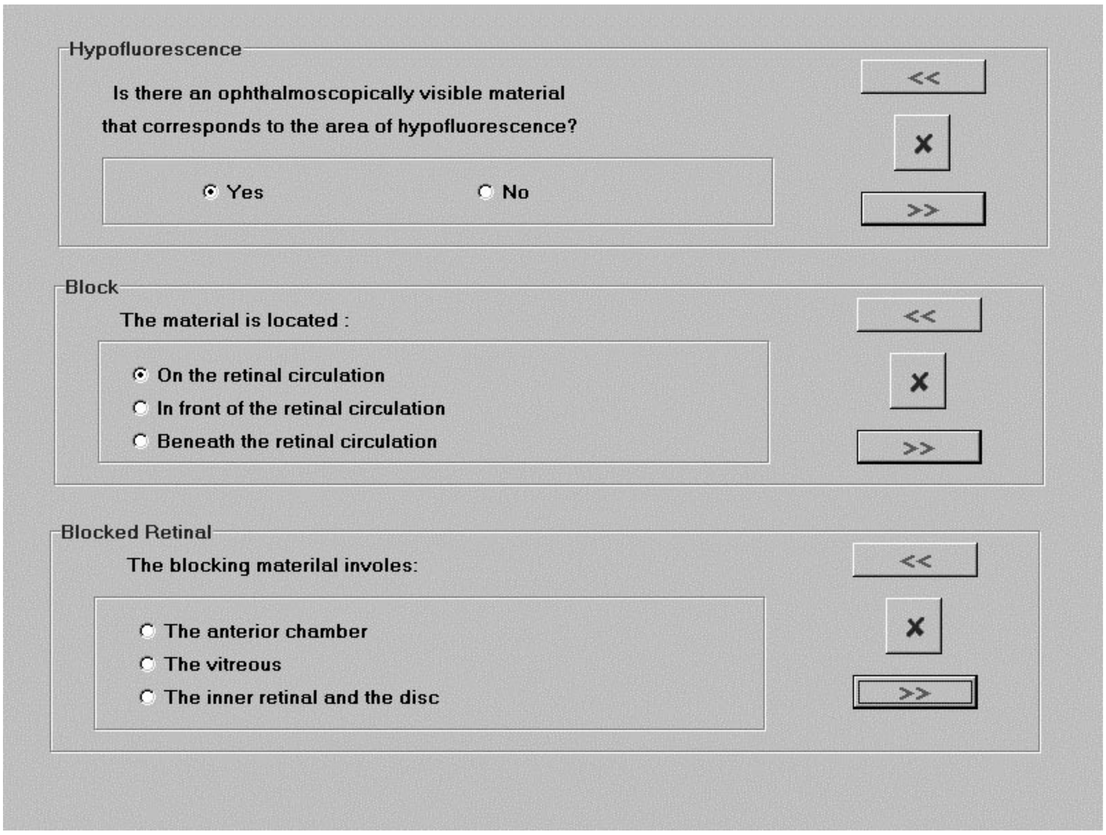

Figure 6: Hyperfluorescence, Block and Blocked Retinal forms

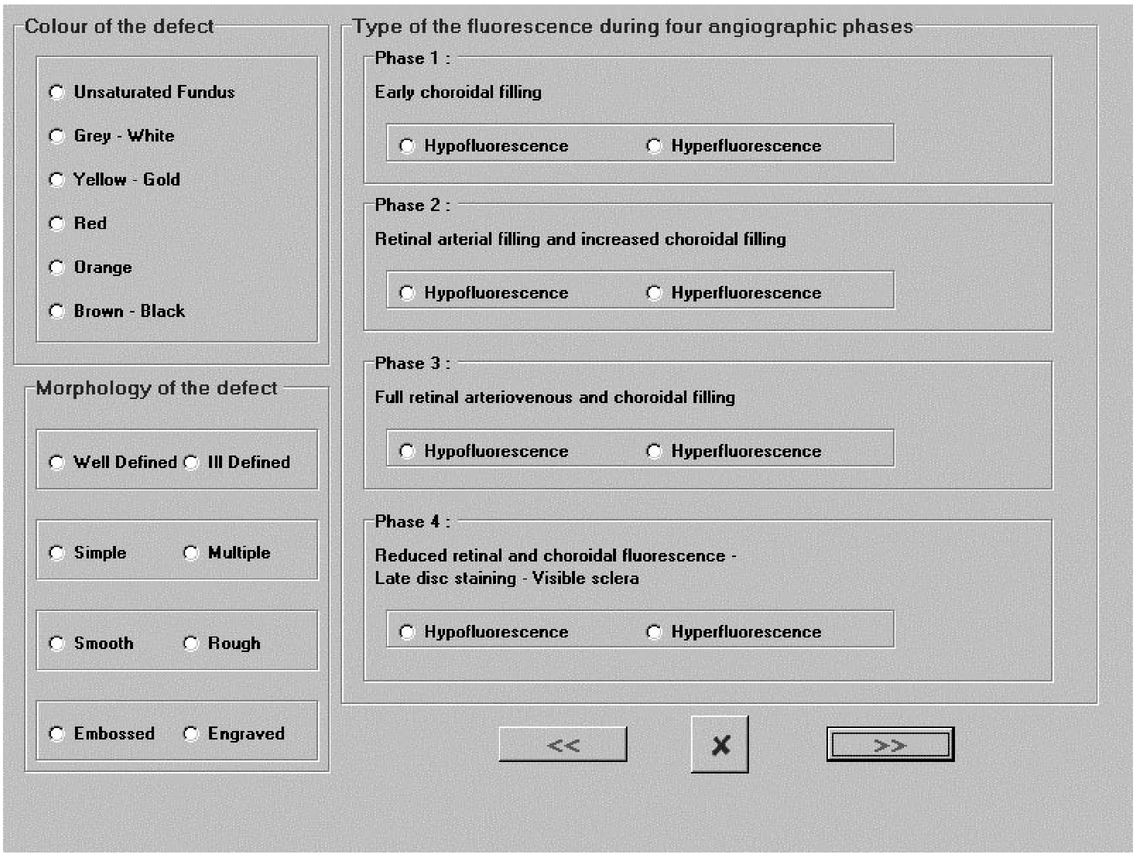

Figure 7: Abnormality Characteristics form

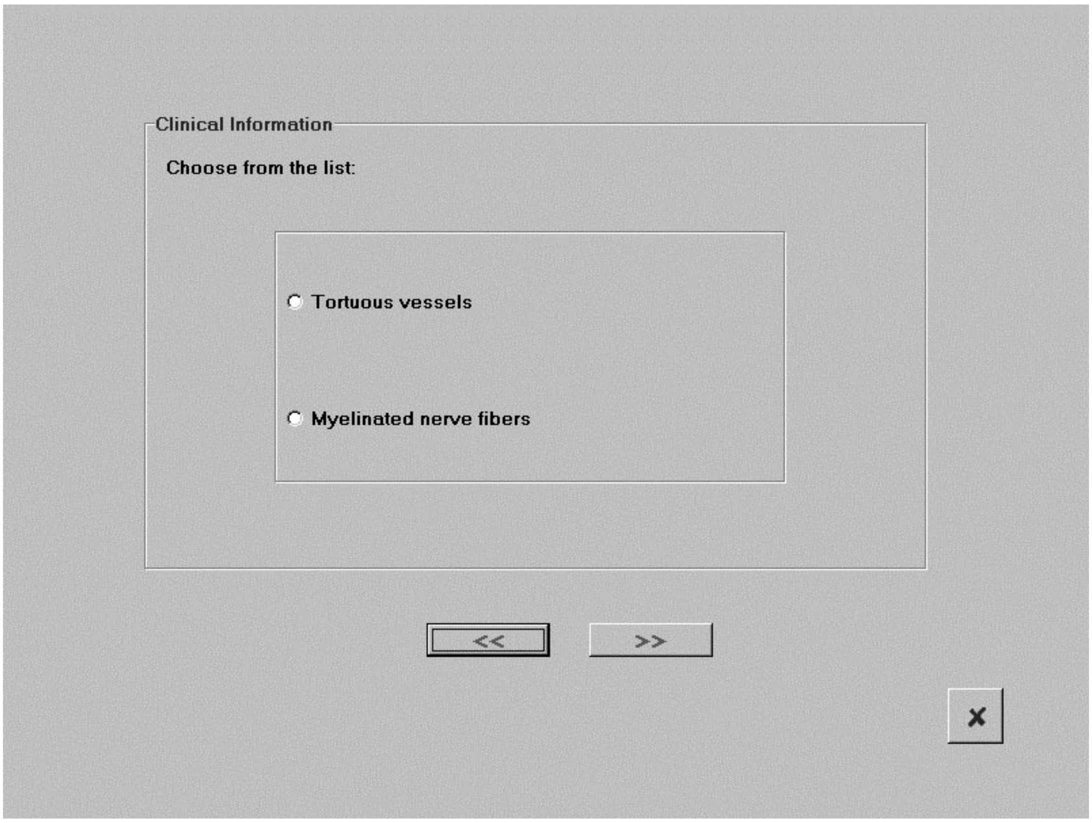

Figure 8: Clinical Information Characteristics form

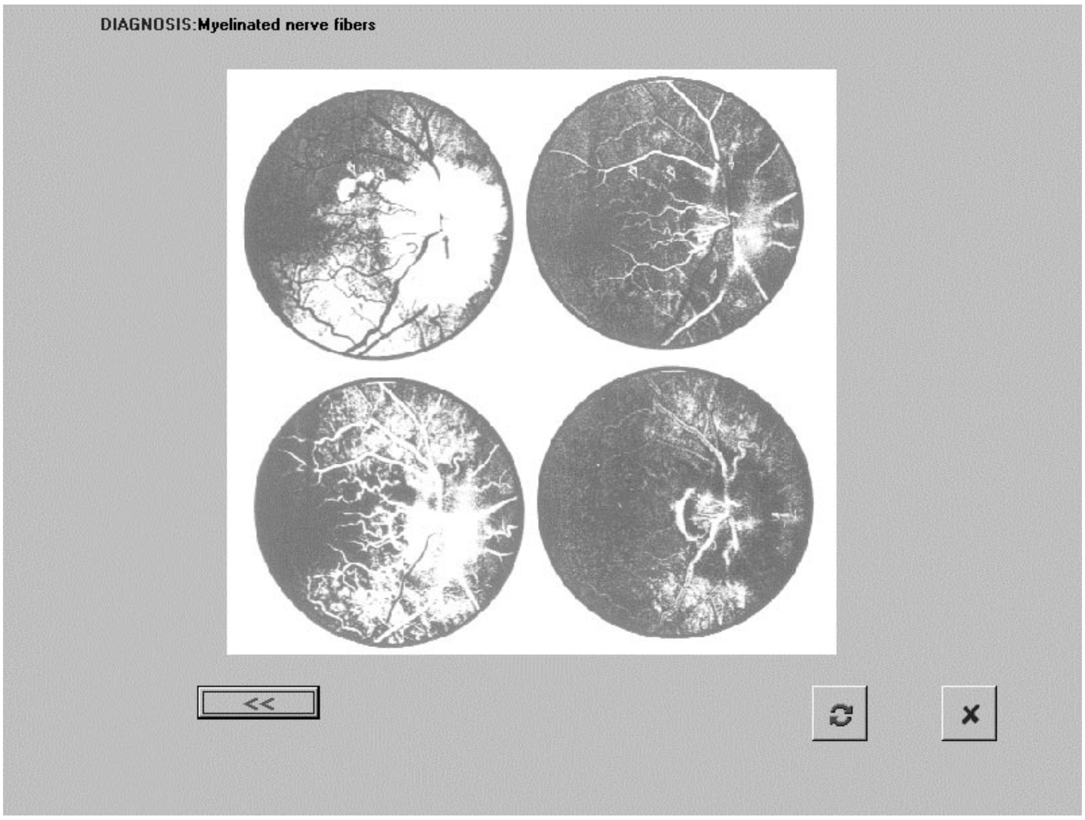

Figure 9: Diagnosis form