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### 1. Introduction

This report describes the proposed MIRACLE database structure for annotation of follicular lymphoma (FL) microscopic images by expert physicians as well as the Web application that was created by CERTH to enable physicians to create, edit and delete annotations on patient's images. The application is available at <a href="http://195.251.117.47/miracle">http://195.251.117.47/miracle</a> and it was developed using PHP language and JavaScript and is currently hosted by ITI-CERTH. Possible future uses of this annotation database include: a) storage and management of sequences of images from patients, along with all associated annotation/grading data, b) statistical analyses on FL data, c) evaluation of grading algorithms for FL images, d) improvement of the performance of FL algorithms by using information available on the database, and e) use of external automatic or semi-automatic annotation tools (e.g. implemented in MATLAB) for the training of clinicians or the enlargement of the database with the addition of automatically-generated annotations.

For the development of this database and application we received input a) from researchers in the Ohio State University who have developed a similar image database and b) from cooperating expert physicians from the Medical School in Aristotle University of Thessaloniki. Also, the same physicians provided sample images with annotations to be included in this database.

In Section 2, an overview of the MIRACLE database structure is provided, while in Section 3 the Web application for annotation of HPF (high power field) images is described in detail. Discussion and future work are provided in Section 4.

# 2. The MIRACLE database

The MIRACLE database was created in MySQL and currently contains 5 tables, as shown in the database schema below (also showing table relationships):



Figure 1 The MIRACLE database schema consisting of five MySQL Tables for: users, patients, hpf\_images, notes (annotations) and login\_attempts.

More specifically, the Tables and their fields are described below:

### Table USERS

Stores the properties of the users of the application (expert physicians) and contains the following fields:

'id' - auto increment (primary key)

'username' - username

'email' - email of the user

'password' - 128 byte encoded password,

'salt' - 128 byte random data for password encoding,

'hash' - not used,

'active' - integer field for account activation (0-not active, 1-active),

'First Name' - First name of the user,

'Last Name' - Last name of the user,

'Profession' - List of codes for the users (0-'Doctor',1-'IT Personnel'),

'Speciality' - List of codes for physicians (0-'histopathologist',1-'Haematologist',2-'Other'),

'Experience on lymphomas' - Classification of experience (0-'Yes',1-'No'),

'Activation' - not used,

#### Table PATIENTS

Contains the properties of the patients whose images are stored in the database and consists of the following fields:

'patient\_id' - auto increment (primary key),

'first\_name' - First name of the patient,

'last\_name' - Last name of the patient,

'age' - Age of the patient,

'gender' - Gender of the patient ('Male'/'Female'),

'comments' - Comments about the patient,

#### Table HPF\_IMAGES

Contains the properties of the images stored in the database and consists of the following fields:

'image\_id' - auto increment (primary key),

'patient\_id' - index to the corresponding patient,

'filename' - filename of the image after its upload to the system (generated by concatenating the image\_id, a dash and the original filename during the upload,

'width' - image width,

'height' - image height,

'magnification' - magnification used (0-'25',1-'40',2-'100',3-'200',4-'400'),

'stain' - type of stain used (0-'H&E',1-'IHC'),

'thickness' - thickness used (e.g. 4µm or 2µm),

'recording\_system' - information about the recording system,

'recording\_date' - date of the recording,

#### Table LOGIN ATTEMPTS

Stores the properties of the login attempts that a user makes and contains the following fields:

'user\_id' - index to the user that logged in,

'time' -time that the user logged in,

#### Table NOTES

Stores the properties of the notes (annotations) made by the clinicians on the HPF images and contains the following fields:

'image\_id' - index to the corresponding HPF image,

'note\_id' - auto increment (primary key),,

'user\_id' - index to the user that made the annotation,

'left' - x-coordinate of top-left corner of the Bounding box,

'top' - y-coordinate of top-left corner of the Bounding box,

'width' - width of the Bounding box in pixels,

'height' - height of the Bounding box in pixels,

'text' - Annotation comment,

'celltype' - type of Cell ('-Centroblast", 'Immunoblast'or "Non-malignant")

'confidence' - Confidence for the Annotation ('Low', 'Medium', 'High'),

## 3. Description of the Web Application for Annotation

The application is accessible only by registered users who have to enter their credentials in the main Login page:



Figure 2 - The Main Login page

The Registration page is presented below:

🗋 Secure Logi	n: Registration ×	
← ⇒ C	195.251.117.47/miracle/register.php	
• Userna • Emails • Passw • Passw • • •	ter with us ames may contain only digits, upper and lower case letters and underscores s must have a valid email format ords must be at least 6 characters long ords must contain At least one upper case letter (AZ) At least one number (09) password and confirmation must match exactly	
Username:		
Email: root		
Password:		
Confirm pas Register	sword:	
Return to the	e <u>login page</u> .	

Figure 3 – The Registration page

However, before a registered user can access the application, he/she has to be activated by the administrator (otherwise the message "Error Logging In or Account not Activated!" appears in the Login page:



Figure 4 – The Error message if an authentication fails or if the user is not activated

Activation is currently performed manually by emailing to ITI-CERTH (<u>ngramm@iti.gr</u>) who can then activate the user in the MIRACLE database. After activation, the user views the main menu of the application:



Figure 5 – Main menu of the application

From the "Manage patients" page, the user can add, edit or delete data for the patients available in the database. A sample "Patient management" page is presented below:

Patients page ×
← → C 🗋 195.251.117.47/miracle/patients.php
First Name:
Last Name:
Age:
Gender: Male •
Comments:
add
Steve Jones 18 M test Edit Delete
Jonh Smith 49 M Edit Delete
<u>Return to main menu</u> .
If you are done, please log out.

Figure 6 – Sample "Patient management" page

By entering the required information at the top (First/Last name, Age, Gender and optional comments) and pressing the add button the user can add a new patient in the database. Below the "add" button the user can see all existing patients and for each record, buttons "Edit" and "Delete" are available, to edit or delete records respectively. A sample edit page is presented below:

Patients p	page ×
← → C	195.251.117.47/miracle/view_patient.php?patient_id=2
First Name:	Steve
Last Name	Jones
Age	18
Gender	Male •
Comments	test
	save

If you are done, please log out.

Figure 7 – Sample "Edit" page in patient management

The second option in the main menu allows the user to upload images to the system and associate them with a specific patient. The "Image Upload" page is presented below:

🗅 Upload image page 🔹 🔪 💽	
← → C 🗋 195.251.117.47/miracle/upload_form.php	
	Upload form
	File to upload: Επιλογή αρχείου Δεν έχει επιλεγεί κανένα αρχείο Please associate the image with one patient
	Press to Upload me!
Return to main menu.	

Figure 8 – Image upload page

The user simply selects the image file to upload to the server and the corresponding patient and then presses the "Upload me" button to start the upload. If the upload is successful the message "Upload was successful" appears.

🗅 Upload success x			
← → C 🗋 195.251.117.47/miracle/upload_success.php			
	File upload Congratulations! Your file upload was successful		
Press here to return to main page.			
If you are done, please <u>log out</u> .			

Figure 9 – Successful Image upload

The third option in the main menu allows the user to view existing annotations made by other users (expert physicians). By pressing 'View annotations', the following page appears:



Figure 10 – View existing annotations menu

The user has the ability to view annotated images for a specific patient or for all patients. He can also select to view annotations created by all users (default) or by a specific expert. After pressing the "Select" button the following list of available annotated images appears:



Figure 11 – Select to view annotations for a specific patient

After selecting the desired image, the user is transferred to the following page in order to view the annotations made by the specific user(s) that he specified:



<u>Return to main menu</u> If you are done, please <u>log out</u>.

Figure 12 – View annotations page

The fourth option in the main menu allows the user to annotate cells in a specific image. By pressing 'Annotate cells' a list of existing patients is presented and then the user can browse the images of a specific patient or simply browse the entire image database. After selecting a specific image the following page appears:



Figure 13 – Cell Annotation page

In this page, the user can see the image he selected and review all existing annotations that he made and/or create new annotations. Specifically, the annotations that he already made appear as rectangles on the image and by clicking them the following widget appears:

			100	E.
1				
3	CentB •	High •		
	📀 ОК	🔵 Delete	💢 Cancel	00

Figure 14 –Annotation widget

In the top part of this widget, the user can view/modify the position and dimensions of a rectangle, which should be positioned by the user so as to define a bounding box of the specific nucleus/cell that needs to be annotated. In the region below, the user can enter comments that will be associated with the specific annotation, while with the two selectors below the user can specify a) the type of cell (Centroblast, Immunoblast or Non-malignant) and b) his confidence for this annotation (Low, Medium, High). Finally, with the three buttons in the bottom of the widget, the user can:

- a) Save the information to the database (with the "OK" button)
- b) Cancel the changes for this particular annotation (with the "Cancel" button)
- c) Delete the specific annotation from the database (with the "Delete" button)

Similarly, in order to create a new annotation, the user clicks on the "Add Annotation" button below, and a new widget (same as the aforementioned) is created at a default image position near the top left corner of the image. The user should then use this widget to properly define the bounding box of the desired cell/nucleus in the image.

With the last option of the main menu, the user has the ability to select an image (of a specific patient) and delete the specific image and all associated annotations made by the users of the web application on this image.

### 3.1 Technical notes

The MySQL database and the web application were developed by CERTH in PHP and JavaScript. The following open source scripts have been used in the implementation:

- a) The script in [1] was used to create the scripts for the authentication of users. A modification has been implemented to support the activation by the administration of a specific user account that has already been registered.
- b) The script in [2], which is an extension (fork) of the open source script [3], was used for annotating images based on the popular JQuery JavaScript library. The specific extension uses AJAX to communicate with PHP scripts that are able to read/write/delete entries from a database. These scripts were integrated and extended to support additional functionalities required by MIRACLE, e.g. adding the "cell type" and "Confidence" fields.

Minimal use of CSS was made while developing the application, as the emphasis was on properly implementing the required functionalities, rather than improving the appearance and attractiveness of the generated pages.

## 4. Conclusions and Future work

We believe that the developed application provides a very stable basis on to which further extensions can be built, to name a few:

a) evaluation of grading algorithms for images of follicular lymphoma,

b) the use of data from this database to improve the performance of follicular lymphoma algorithms,

c) Storage and management of sequences of images from patients, along with all associated annotation/grading data,

d) Use of external automatic or semi-automatic annotation tools (e.g. implemented in MATLAB) to provide additional computer-generated annotations of HPF images in a database,

e) Statistical analyses,

f) Training or early stage physicians.

Note that most of the code developed in MIRACLE is written in MATLAB and access to MySQL databases via MATLAB is very easy using the "Database" toolbox provided by Mathworks. Therefore, we believe that future applications (like the above) that make use of and extend the MIRACLE database are easy to implement.

### 5. References

- [1] How to create a secure Login script in PHP and MySQL, http://www.wikihow.com/Create-a-Secure-Login-Script-in-PHP-and-MySQL
- [2] jQuery Image Annotate fork, <u>https://github.com/stas/jquery-image-annotate-php-fork</u>
- [3] jQuery Image Annotate, <u>https://github.com/flipbit/jquery-image-annotate</u>