Automated Retinal Image Analysis over the Internet

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***Abstract*—Retinal clinicians and researchers make extensive use of images, and the current emphasis is on digital imaging of the retinal fundus. The goal of this paper is to introduce a system, known as RIVERS (Retinal Image Vessel Extraction and Registration System), which provides the community of retinal clinicians, researchers, and study directors an integrated suite of advanced digital retinal image analysis tools over the Internet. The capabilities include vasculature tracing and morphometry, joint (simultaneous) montaging of multiple retinal fields, cross-modality registration (color/red-free fundus photographs, and fluorescein angiograms), and generation of flicker animations for visualization of changes from longitudinal image sequences. Each capability has been carefully-validated in our previous research work.**

The integrated internet-based system can enable significant advances in retina-related clinical diagnosis, visualization of the complete fundus at full resolution from multiple low-angle views, analysis of longitudinal changes, research on the retinal vasculature, and objective, quantitative computer-assisted scoring of clinical trials imagery. It could pave the way for future screening services from optometry facilities.

***Index Terms*—internet-based, registration, alignment, retinal image analysis, vasculature tracing.**

1. Introduction

Retina-related clinical procedures and research studies are largely image driven. The current emphasis is on digital imaging of the retinal fundus, due to its high quality, flexible visualization, low cost, speed, ease of archival, transmission and retrieval. Low-level processing tools for image display, enhancement, manual annotation, and manual image analysis are now commonly integrated into fundus imaging systems. The focus of this paper is on an integrated, internet-based system (http://www.vision.cs.rpi.edu/RIVERS/) which aims to make available a set of high-quality, accurate, and highly-automated image analysis tools to retinal clinicians and researchers, with an initial focus on certain broadly applicable operations. Some examples of such operations are noted below:

- Automated Vessel Tracing: A researcher studying the retinal vasculature can use automated, accurate, detailed, and objective traces of the fundus vasculature (Figure 1), instead of manual traces. For instance, the reader can make quantitative measurement of veins and arteries to monitor the effect of treatment.
- Automated Sub-pixel Accuracy Registration (Alignment): Intra- and inter-modality registrations (Figure 2) are often performed for diagnosis and pre-surgical planning. Retinal fundus images are challenging to align due to the unknown curvature of the fundus, as well as the patient-dependent optical characteristics of the eye, coupled with camera distortions.
- Visual Change Analysis: This is achieved by visualizing the results of registration of retinal images taken at different times as a flicker animation [1]. It is common to compare images of a fundus taken before and after an intervention for clinical practice and in support of clinical trials. It is also common to track changes over longer periods in longitudinal studies such as AREDS (Age-Related Eye Disease Study) [2], and the Wilmer geographic atrophy study [3].

Automated Montaging (Mosaicing): Study of retinal areas that are wider than the view of the instrument without sacrificing spatial detail requires the ability to "stitch together" overlapping partial views into a synthetic wide-angle view (Figure 3). For example, diabetic retinopathy studies can benefit from montages [4]. When extended regions of the retina must be studied for changes, it becomes necessary for entire montages of different visits to be aligned, and then displayed as a moving animation on a computer screen to visualize changes over time.

During the past decade, this group has contributed significantly to each of the above areas, having developed, integrated, clinically-validated, and continually refined algorithms [5-14]. The algorithms have reached a sufficient level of maturity, robustness, speed, quantitative accuracy, software system stability, and automation level that broader uses can be attempted.

This paper describes an integrated, carefully-engineered

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implementation of these image tools in a manner that allows them to be accessed over the internet by the retina community (Figure 4). Named RIVERS (Retinal Image Vessel Extraction and Registration System), the intent of this system is to make available these unique high-quality, accurate, quantitative, and highly-automated image analysis tools to retinal clinicians and researchers, with the intent of advancing the field.

2. Background and Related Literature

Vessel tracing is the process of automatic vessel delineation/tracing by the computer. A comprehensive review can be found in [15]. The technique adopted by the RIVERS system is recursive tracing of the vasculature based on a localized model [9,12]. Of particular importance is the detection and morphometry of vascular bifurcations and crossovers, which strongly influence the registration accuracy if serving as landmarks. This has motivated the development of specialized algorithms for precise and repeatable extraction of the bifurcation/crossover locations [8], and RIVERS incorporates these advances.

Retinal image registration algorithms in the literature can be classified as grayscale based [16,17] and feature based [5,6,13,18,19]. The latter are much faster. The algorithm incorporated in the RIVERS system is the Dual-Bootstrap ICP algorithm, introduced by Stewart et al. [6], which uses the 12-parameter quadratic spatial transformation model.

The literature on automated mosaic synthesis is extensive [7,14,20,21]. Adopted by RIVERS is the technique of joint registration [7], which ensures corresponding vessel centerline points from multiple pairwise registrations to be mapped consistently to the anchor image for higher registration accuracy, and allows successful alignment even for image pairs that failed in pairwise.

Berger et al. [1] introduced the dynamic flicker animation as an effective tool for visualizing changes in the retinal fundus. In this method the two registered images are displayed in rapid succession, usually a few seconds apart. Changed regions in the image appear to flicker, whereas unchanged regions appear steady. The RIVERS system incorporates this practically-useful feature.

Notwithstanding the recognized potential of the higher-level digital image analysis algorithms described above, as well as the published literature on algorithms noted above, clinicians are hampered by the sparse availability of such computational tools in comparison to the need. EyeCheck [22] is one of the simplest, serving patients by transporting their fundus photographs and related data to/from remote physicians who provide diagnosis for conditions such as diabetic retinopathy. TOSCA [23] is a web-based retinal image alignment tool that requires manual landmarks specification by the user. The alignment algorithm only compensates for image translation and rotation, and has restrictions on image dimensions and field of view. RetinaView [24] is also a web-based tool, but the focus is on segmentation of pathologies, such as drusen and microaneurysms. Inter-modality registration is performed for display of segmentation results of different modalities.

Among tools that are not designed for use over the Internet, AutoMontage (Ophthalmic Imaging Systems Inc., United States) [25] is a commercial montage tool that aligns images with the anchor image. The image transformation model in this product is much simpler compared to the 12-dimensional matrix used by our software, and the accuracy is lower. The effect of applying a correct model is reported in [6]. Other commercial packages known to us include: (1) Retinalyze System (Horsholm, Denmark) for detecting potential lesions from fundus images [26], (2) ImageNet 2000 Mosaicing Software bundled with Topcon Inc. Retinal Camera (Tokyo, Japan) [27], (3) VISUPAC [28] Software, an image analysis tool extracting qualitative information from fundus images, (4) Alignment software bundled with ARIS (Automated Retinal Imaging system) developed by Visual Pathways Inc. (Sacramento, CA) [29], and (5) Heidelberg Retina Angiograph, which is a digital scanning laser ophthalmoscope, with the capability of automatically generating wide-field montages for a number of modalities [30].

3. System Description

The RIVERS software system is designed to run on a centralized server (typically running a variant of the Linux operating system) and be accessed over a computer network using a standard web browser. As illustrated in Figure 4, it has three major components: a front-end interface part written using standard web interface programming languages (PHP and HTML), a set of core image analysis routines implemented using C++, and a back-end image database built on an open-source mySQL query system [31]. The information stored in the database is the result of running the modules, so the users can access the result repeatedly without the cost of re-running the modules.

Each user of this system has a password-protected account and a data storage area. An account can be obtained from the system administrator (retina_web@cs.rpi.edu) free of charge. The user can upload a set of related images to this storage area, and specify a set of desired image analysis operations, along with an optional set of desired choices/settings if necessary. These inputs are processed by the server software, and made available to the user. These results can be visualized on the user's computer screen within a standard web browser program, and downloaded using a graphical and user-friendly web-interface. More functions will be added to the system in the future as they mature.

RIVERS is a fully automatic system, i.e., it does not expect interactive inputs or hints from the user in order to perform its functions beyond specification of the task, specification of the images to be processed, and, occasionally, some (optional) settings. Using the default settings, which are applicable to a wide range of image resolution, the average number of click per task is 2 (one to specify and one to trigger the task). Given a set of images, the system first identifies salient features for alignment, essentially vessel centerlines and bifurcation/crossover points. This is achieved by the "vessel detection" operation. Using the set of salient features, the system estimates the best alignment between every image pair, and then jointly aligns all images. The result of the “image alignment” operation is a set of mathematical mappings that take points from one image to another. To make such mappings useful to physicians, both “montaging” and “montage animation” operations convert the mappings to dynamic visual flicker animation outputs for easy interpretation. Sample outputs of the operations are available at the RIVERS website. A screen dump of the interface is shown in Figure 4(b). The tabs for the operations are ordered from left to right in the order of execution. The user may trigger the operations in the order specified if fine-tuning is desired, or directly visit the target operation, using default settings for the precursors.

3.1. Vessel Detection Module

The vessel detection module generates automated tracing of the vessel centerlines and analysis of bifurcation and crossover locations. The results of the operation are centerline locations, vessel boundary locations, and bifurcation/crossover locations, as shown in Figure 1. All three types of features are used at different stages of the alignment process --- landmarks for initialization, and centerlines and boundaries for refinement.

The output of the vessel detection module includes both visual and numerical data. For visual inspection, the detected vessel traces are drawn as an overlay on the original images as illustrated in Figure 1(a) and 1(b). For quantitative analysis, the numerical data underlying these traces are stored in a plain text file. A sample fragment of this textual output is also shown is Figure 1(c). This numerical output is available to the user and is versatile for analysis of vascular properties and their changes.

As a general guide to the robustness of vessel detection, we reproduce some measures reported in our previous publications in the engineering literature [8,9,11]. The repeatability of the landmark (crossover/bifurcation) location is 1.07 pixels. For the repeatability measure of the vessel width, the mean width difference is 0.44 pixel. Using the standard (default) settings, a validation study using a multi-observer gold standard showed a 94% completeness and 35% false positive rate for vessel detection.

3.2. Image Alignment/Registration Module

The output of image registration is a 12-parameter spatial transformation linking a pair of images. Figure 2 shows the result of registration of a sample pair of multi-modality images, and the associated numerical data describing the spatial transformation. Given a point $p=(x,y)$ in one image, the spatial transformation Θ generated by registration allows one to locate a corresponding point $q=(x',y')$ in the second image using the following simple matrix formula:

$$\begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} \theta_{11} & \theta_{12} & ...\theta_{16} \\ \theta_{21} & \theta_{22} & ...\theta_{26} \end{bmatrix} \begin{bmatrix} 1 & x & y & x^2 & xy & y^2 \end{bmatrix}^T$$

The numbers in Figure 2(b) include the centerline error measure (CEM) indicating the precision of the alignment in units of pixels, the stability (higher values are better), and the parameters of the transformation. CEM is computed as a weighted average of the alignment errors over the overlapping region between the two images, where the alignment error for a vessel centerline point p is given by the distance between its transferred location and the closest centerline point in the second image. A pair-wise registration is considered successful if its CEM falls below a threshold value.

To provide the reader a feel for alignment performance, we summarize some results below. In one study [10], algorithms were validated with a large set of over 800 color fundus images representing five common pathological conditions: healthy, dry and wet age-related macular degeneration, diabetic retinopathy, and vein occlusion. When the CEM threshold was set to 1.5 pixels, the system successfully aligned 99.9% of the image sets taken during the same patient visit, and 90% for images of different visits. In the same study, 61 fluorescein angiogram (FA) sequences were tested. The circulation of fluorescein defines 5 consecutive FA phased: arterial, arteriovenous, venous, late venous, and recirculation. All sequences were successfully jointly-registered up to the venous phase, and 75% reached the recirculation phase.

3.3. Montaging and Animation Modules

The notion of “patient visit” is important for montaging. The user is enabled to build a single montage containing all images, or one montage per patient visit, using the joint registration process previously mentioned. The latter capability is useful for study of longitudinal changes. In either case, the user can specify one image that forms the anchor for the montage. This image undergoes the least amount of warping as the montage is constructed (Figure 3).

The accuracy of the montage synthesis is guided by the CEM threshold value specified by the user, or the standard value of 1.5 pixels assumed by the system otherwise. Ordinarily, this threshold is only applicable to images from a single visit. When the montage is constructed from images taken during different visits, the CEM value is automatically relaxed by the system to twice the user-specified value. Without this relaxation, it was found that several fundus fields, especially those acquired during a different patient visit compared to the specified anchor image, would not be included in the montage synthesis. The most common reason for such exclusion is alignment error resulting from changes in the retina.

Another application of image registration is the composition of a video sequence (animation) consisting of registered images or entire registered montages. An animation provides the physicians a better mechanism to visualize changes and blood flow over time. Our system also enables only the common region of the set of alternated images or montages to be displayed, and construction of seamless montages (Figure 3(b)).

4. DISCUSSION

The focus of the current RIVERS system is on integration of computational tools for vessel detection, image alignment, and its direct application on montaging and flicker animation to make them freely accessible to physicians and researchers over the Internet. In future work, the group expects to integrate more disease-specific processing modules. One area of emphasis is incorporation of recently-developed automated change analysis algorithms that quantify and classify a variety of vascular and non-vascular retinal changes in a manner that is robust to illumination variations [32]. The main advantage of the internet-server based approach is to provide the opportunity for continuous improvement of the core algorithms, driven by performance data over images from diverse sources. With appropriate improvements, this system can become an assistive tool for research studies and clinical trials.

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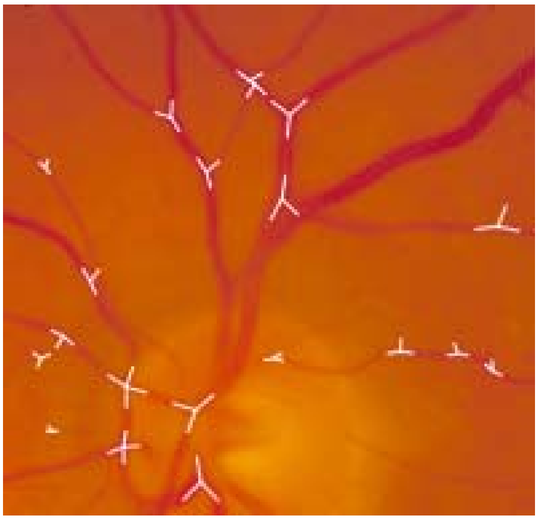
(a)

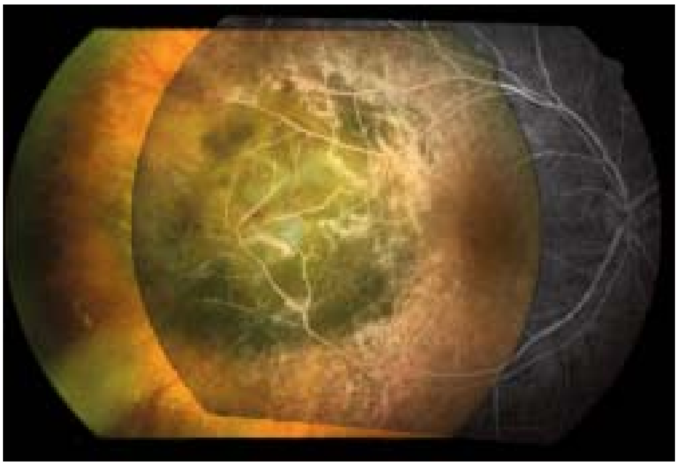


(b)

TRACE_RESULT
image_id = 000000A1.pgm
TRACES
93 [93 traces in total.]
6 3.4878 -1 0
[6 trace points. Average width 3.4878. End landmark index 0, and no begin landmark (-1).]
282.717 4.08986 13 3.63491 81.5
[Point location 282.717, 4.08986. Tangent direction index 13. Width 3.63491. Strength 81.5.]
282.205 6 13 3.52067 74
281.61 7.97851 4 3.42757 150
281.295 10 4 3.42956 80
….
LANDMARKS
31 [31 landmarks]
881.916 44.9013 -1 10.5667 3
[Landmark center Location 881.916, 44.9013. Radius 44.9013. 3 vessels intersecting.]
-0.944338 -0.328977
[direction of vessel #1]
0.394302 -0.918981
[direction of vessel #2]
0.255318 0.966857
[direction of vessel #3]
…

(c)

Figure 1: Sample vessel segmentation (tracing) results overlayed on fundus images: (a) automatically-generated vessel centerline traces near the optic disk; (b) automatically detected bifurcation/crossover points. (c) The numerical data for this sample image. The blue text represents our explanatory comments of selected lines in the computer output. Traces are represented by the vessel centerlines. The landmarks refer to vascular bifurcations/crossovers **.** (Images from Center for Sight, Albany, NY)



CLE = 0.689518; [centerline error measure]

stability = 0.011105; [higher is better]

xform = 3; [12-parameter transformation]

[41.6736, -0.61349, 0.0957902,

0.00186172, 0.00115392, -0.00299497];

[1st row of Θ]

[484.67, -0.760376, 0.10636, 0.000636505,

0.00085849, 0.0027404];

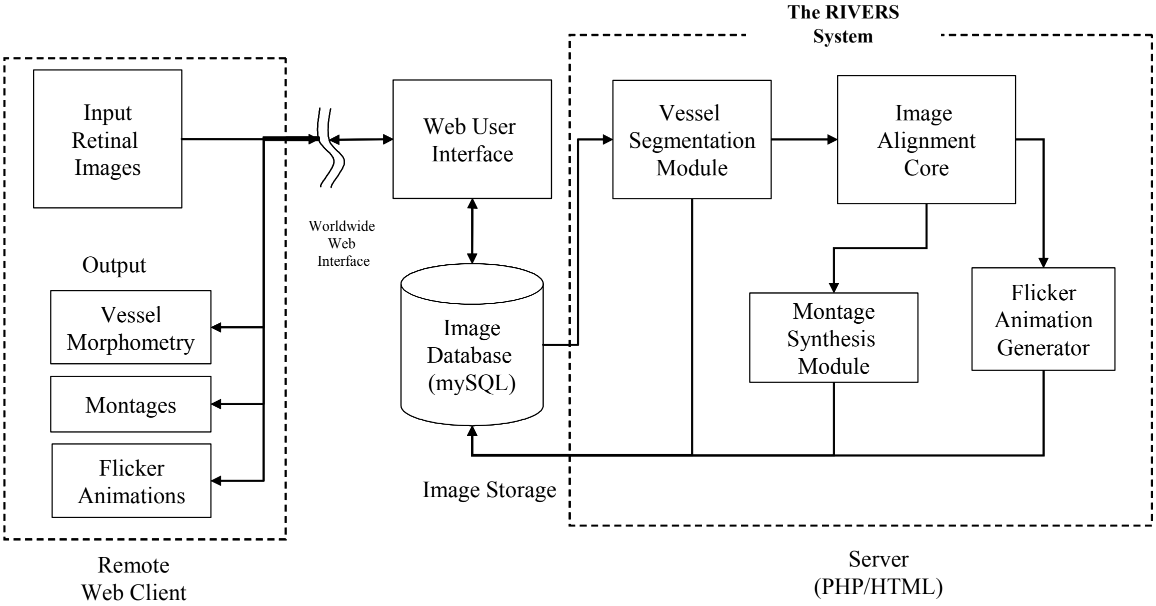
[2nd row of Θ]

(a) (b)

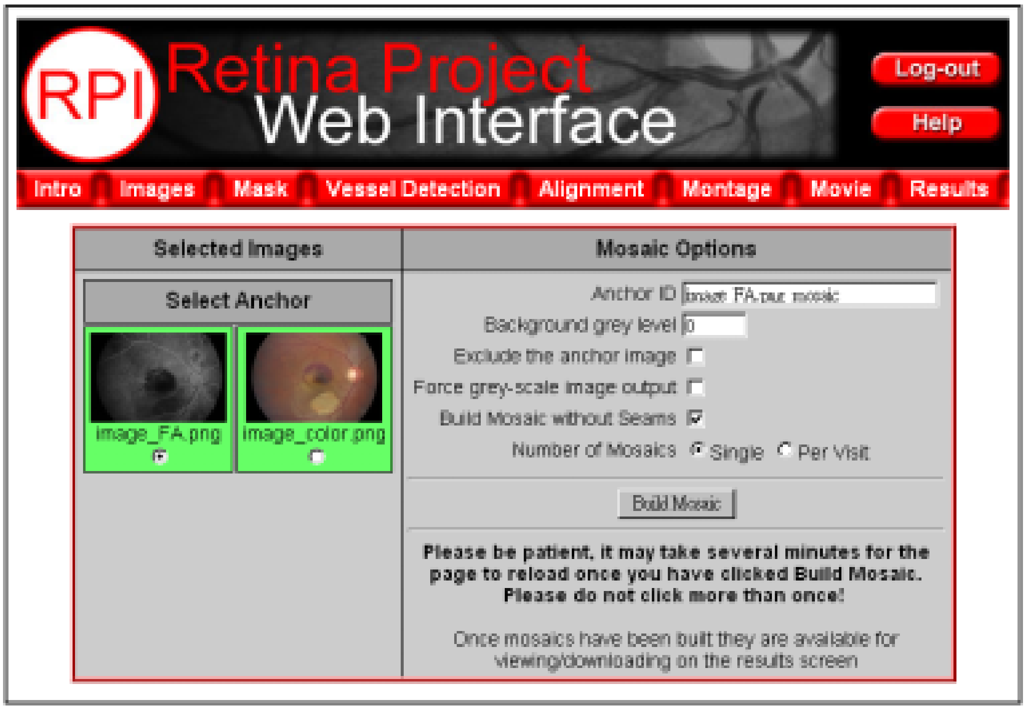
Figure 2. Illustrating automated pairwise registration of a color fundus image with a fluorescein angiogram for an eye exhibiting ocular melanoma. (a) The automatically synthesized montage, used as a tool to visualize the alignment. (b) Numerical registration data with explanatory annotations in blue text. (Images courtesy Dr. James Handa, Wilmer Eye Institute)

(a) (b)

Figure 3. Sample montages of 4 pathological images with the anchor image labeled. Any of the field can be designated as the anchor by the user. (a) Montage with Image A as the anchor with the blending turned off to show the boundaries of the original images. (b) Blended montage with Image B as the anchor allows seamless visualization. (Images from Center for Sight, Albany, NY)



(a)



(b)

Figure 4. Main components of the RIVERS system. (a) Retinal fundus images are sent to the RIVERS server over the internet, using a standard web browser, and placed in an image database. The server accepts additional user inputs and generates the three main types of presentations to the user, which can be viewed, downloaded and saved by the user. (b) A sample of user's view screen of the "Montage" page. (URL: http://www.vision.cs.rpi.edu/RIVERS/)

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