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TissueWiki^{Mobile}: an Integrative Protein Expression Image Browser for Pathological Knowledge Sharing and Annotation on a Mobile Device

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Abstract

Doctors need fast and convenient access to medical data. This motivates the use of mobile devices for knowledge retrieval and sharing. We have developed TissueWiki^{Mobile} on the Apple iPhone and iPad to seamlessly access TissueWiki, an enormous repository of medical histology images. TissueWiki is a three terabyte database of antibody information and histology images from the Human Protein Atlas (HPA). Using TissueWiki^{Mobile}, users are capable of extracting knowledge from protein expression, adding annotations to highlight regions of interest on images, and sharing their professional insight. By providing an intuitive human computer interface, users can efficiently operate TissueWiki^{Mobile} to access important biomedical data without losing mobility. TissueWiki^{Mobile} furnishes the health community a ubiquitous way to collaborate and share their expert opinions not only on the performance of various antibodies stains but also on histology image annotation.

Keywords

histological image; mobile medical device; image annotation; knowledge sharing

I. Introduction

With advances in the past decade, mobile devices have increasingly drawn the attention of the medical research community. They provide users with a just-in-time solution to access to and process important medical knowledge. In this paper, we introduce our application called *TissueWiki^{Mobile}*, which provides a mobile-based platform to browse and process online cancer-related knowledge. TissueWiki^{Mobile} communicates with our web-based TissueWiki, which currently contains data from the Human Protein Atlas and is being expanded continuously to provide relevant clinical meta-data for different interest groups. Thus, TissueWiki^{Mobile} provides a ubiquitous cancer research extension to TissueWiki.

In this section, we address the current state of mobile medical application. Then we introduce the background of TissueWiki^{Mobile} in section II. Section III proposes the architecture, prototype, and the capabilities of the tool. Section IV focus on the tool's

usability and the evaluation of system performance. We finally make our conclusions in section V.

A. Need for Ubiquitous Medical Imaging Platforms

Recent advances in both computing hardware and software for mobile devices enable portable, high- function extensions to traditional computing platforms. Google Sky Map [1], a mobile extension to Google Sky [2], is a good example that helps people identify the celestial stars and constellations by simply pointing their phone at the sky. These web- and mobile-based tools start a new evolution of astronomy visualization from traditional careful observation using naked eye, to telescopic photographs via a personal computer screen and even a small view on a mobile device.

In addition to telescopic images from far reaches of our marco-universe, people are also eager to explore the micro-universe of the human body using microscopic images. More and more practitioners in health community rely on mobile devices to access important medical images for immediate diagnosis anytime without any spatial constraint. Each medical image should be processed in order to extract insightful information for disease interpretation. By communicating with a central repository that can store and manage images with correspondence knowledge, mobile devices can play a just-in-time role of creating and sharing image content around the world so as to improve the efficiency of disease diagnosis and treatment.

The Picture Archiving and Communication System (PACS) [3] seems a nearest solution to the above repository system. PACSs allow of integration and viewing of information from various sources such as pathology, radiology from different departments. However, PACSs only support Digital Imaging and Communications in Medicine (DICOM) format of a select number of image modalities such as magnetic resonance (MR) and positron emission tomography (PET). There are no known efforts to extend DICOM to histology images so new repositories are needed.

B. Apple iPhone and iPad

The *Apple iPhone* and *iPad* were launched in 2007 and 2010, respectively. TissueWiki^{Mobile} is developed on them in the following considerations. 1) Their software development kits (SDKs) allow developers to easily develop third party applications (apps) and deploy them through the Apple's *App Store* which is the largest online application store in the world. 2) The SDKs provide organized views (e.g. navigation and table views) that can systematically display complex biomedical data. 3) The advanced touch-sensitive screen enables users to interact with images using simple finger operations (e.g. two-finger zooming and one-finger panning) which is ideal for high-resolution medical image browsing. 4) Their wireless network technologies make TissueWiki^{Mobile} be able to seamlessly upload and retrieve data from its central database.

C. Current Mobile Medical Applications

Table I shows examples of knowledge available through mobile medical applications. Unlike TissueWiki^{Mobile}, these applications do not capture expert knowledge from the users in order to realize bidirectional knowledge transfer.

II. Background

A. The Human Protein Atlas

Immunohistochemistry (IHC) is a widely used technique to detect the presence of specific antigens in tissue sections via interaction of labeled antibodies [9- 10]. Several institutes have already worked towards establishing public image resources on the web for antibody information expression. The Human Protein Atlas (HPA) is the largest antibody-based repository for high-resolution tissue microarray (TMA) images [11-12]. Every antibody in HPA contains more than 550 IHC images on 20 types of cancer and 48 normal tissues types from many individual patients. All of the information from HPA is publicly available without issues of security and patient privacy.

B. Image Annotation

Annotation in digital medical imaging is a core medical interpretation method in both the clinical and the research settings [13]. Annotation parameters of IHC images include overall staining, intensity, and localization of immunoreactivity, among others, and should be manually annotated by certified pathologists. In the HPA project, the initial annotation process was performed during a two-day “annotation jamboree” where 26 pathologists annotated 80,000 images using individual desktop terminals [11]. After the workshop, an internet-based system was developed in which a pathologist could download images within an antibody, perform the annotation and finally submit all the information back to the database. A dictionary of the IHC annotations is available on HPA web site [14].

C. TissueWiki

Wikis have become a popular approach to organize complex medical knowledge [15]. In our ongoing endeavor, we have already established a three terabyte database of histology images from HPA and provided an integrative third-party public repository, *TissueWiki* [16]. This system is mainly based on our larger designed system, *ArrayWiki* [17]. The *TissueWiki* portal is shown in Fig. 1. It provides a user-friendly Wiki interface for querying antibodies and presenting their meta-data with all of the images in normal and cancer tissues of all patients. In addition to all of the information imported from the HPA project, we also developed querying tools to help users in validating and ranking of data based on antibody expression and tissue quality. As for IHC images, several signal processing algorithms were implemented in a manner of computer-aided analysis for image quality assessment.

Although the *TissueWiki* webpage can be accessed by the native iPhone browser, *Safari*, the 3.5-inch screen size is not ideal for traditional web pages. Besides, the development tool of Wiki pages, *MediaWiki* [18], does not have a convenient extension for placing annotations on IHC images. Therefore, in this project, we present the *TissueWiki*^{Mobile} app on both iPhone and iPad platforms, which not only features the same basic functionalities as

TissueWiki in browsing meta-data of antibodies and IHC images, but also allows users to create and share knowledge of image annotation.

D. Target Users of TissueWiki^{Mobile}

1) Professional users—By integrating web-based TissueWiki with mobile-based TissueWiki, users of our tool can be professionals of histology imaging data. They could be clinicians (e.g. pathologists), biomedical researchers, and bioinformaticians. For example, clinicians can classify the disease subtype or the patient's subclass by examining the patient's biopsy with references of antibody information and IHC images from the TissueWiki database. Using the TissueWiki^{Mobile}, doctors can annotate the biopsy and IHC images so that the results can be viewed and commented upon by other specialists to form a quick discussion.

2) Public users—Lack of ability to segment jointed clusters of cells (e.g. count 5 jointed normal cells as one giant cell which is misclassified as tumor cell) imposes a real challenge on current computer-based cell counting process [19]. In addition to professional users, TissueWiki^{Mobile} can also be used by general public interested in cancer or cancer biology. Using the cell counting interface, public volunteer can manually segment cells in clusters with minimum training. The cell counting performance is simple, but its result is valuable to improve the accuracy of current computer-based cell counting results.

III. Architecture and Prototype

A. Data Communication with TissueWiki Server

Fig. 2 shows the architecture of the TissueWiki and TissueWiki^{Mobile} prototypes. Both share the same web server in which the database imports antibody knowledge from the HPA using batch processing. TissueWiki is based on open source MediaWiki software from the Wikipedia Foundation. The Wiki HTML layout contains many extra features designed for web browsing on a good network connection (e.g. cascading style sheets and messages for debugging performance problems). Our original application parsed these pages directly, but the performance of menu navigation was slow due to transmission of so much extra data. A stripped-down version of MediaWiki is available that provides better performance on mobile devices, but this version does not offer the touch annotation and enhanced features that we deemed important. We developed PHP: Hypertext Preprocessor scripts to generate Extensible Markup Language (XML) files to provide streamlined data on-demand to reduce the wireless transmission traffic and data loading time. XML technology is widely used in biomedical research, such as imaging [20] and mobile computing in clinical environments [21].

B. Principles of Interface Design

While Shneiderman's "Golden Rules of Interface Design" [22] have exists for some time now, there have been no similar guideline developed for mobile devices [23]. Using existing guideline as a starting point, Gong and Tarasewich proposed a set of practical design guidelines for mobile devices interfaces [23]. The principle of TissueWiki^{Mobile} interface design follows five of the guidelines:

- Offer informative feedback
- Reverse of action
- Design for top-down interface
- Reduce short-term memory load
- Error prevention and simple error handling

C. Capabilities of TissueWiki^{Mobile} on iPhone

The current iPhone app is developed with SDK version 3.1. Fig. 3 illustrates the workflow of the app's operation and interface views. During operation, the app continually requests information from the server depending on the end user's requests. It parses the received XML results into proper views and waits for the next request. When the end user selects one image as a result of a hierarchical antibody browsing, the app can request, cache, and display the original image in a functional browser. During image editing, all created annotations and paths are saved persistently in the local file system. The details of each step are discussed in the following paragraphs.

1) Antibody meta-data browsing—Fig. 4 and Fig. 5 illustrate real views of the corresponding (numbered) steps in Fig. 3. The app's entry view, *Application Entry* (Fig. 4a), provides two options in the bottom for reading the introduction of TissueWiki^{Mobile} and its manual. The top cell, Antibody Browsing, triggers a request to the server (step 1) for all available antibodies, and the results are displayed in *Antibody List* (Fig. 4b). As an antibody has been selected, the app sends a new request (step 2) and displays the received antibody meta-data in the *Antibody Detail* (Fig. 4c). This view categorizes the meta-data into the top four cells (groups) for users to select (step 3). Fig. 4d is an example of the Gene/Protein group of antibody HPA000285.

After selecting an antibody, the bottom two cells of the Antibody Detail view are used to evoke (step 4) two types of lists, *Cancer/Normal List* (Fig. 4e), for the end user to select one tissue type from 48 normal or 20 cancer types. Based on the end user's selection, the app requests all available patients and their corresponding images from the server (step 5). The received results are presented in *Patient List* view as shown in Fig. 4f. Each cell of this view previews the patient's IHC image and several key pieces of meta-data.

After one patient has been selected (step 6) in the *Patient List*, detailed information about the patient and image are presented in *Image/Patient Detail* (Fig. 5a). The top two cells categorize the patient and image information and can be expanded for more detail such as Image Information in Fig. 5b. In addition to the IHC thumbnail image, the *Image/Patient Detail* view also presents several color-based masks generated by TissueWiki.

2) Image browsing and annotation—The app requests for the original image (step 7) when the end user selects one of the thumbnails in the *Image/Patient Detail* view. The received original-sized image is displayed in the *Image Browser* as shown in Fig. 5c. A stamp in the view's lower left indicates the affiliation of the current image, which helps users to track where they are after such a long hierarchical interaction. It also indicates the

patient's gender, age, and disease. The two buttons in the top right corner are provided for detailed patient (P) and image (I) information as we have seen in Fig. 5b. The *Black* button in the view's bottom middle allows the end user to select one from eight different colors for annotations and paths. The title of the button reflects the current selected color.

The *Annot* button allows the end user to place annotations on the image. Instead of adding free text on or outside the tissue, the app places a footprint where the end user taps. The footprint contains the corresponding sequence number. When the end user taps again on the footprint, the annotation can be viewed and edited, or deleted if created improperly. If the end user chooses to edit the annotation, the *Annotation Form* is provided (Fig. 5f). This form consists of several key options for the end user to fill such as microscope artifact, necrosis, and normal gland. One “Other” option is given for other comments.

The image browser also allows the end user to add hand-drawn paths when the *path* button has been selected. Fig. 5d is an example where one annotation and one path are placed on the image. A footprint with sequence number is also provided at the end of each drawing. By tapping the footprint, the path can be deleted in case it is drawn improperly. All of the annotation information is stored persistently; thus, next time the end user can continue the image editing by retrieving all the data created previously.

Finally, when the *Pan* button has been selected, the image can be panned by one-finger scrolling or zoomed by two-finger pinching for better image viewing. We also provide a switch in the bottom left of the view to hide all created annotations and paths, resulting in a clean canvas.

3) Manual cell counting—As mentioned, one goal of the tool is to provide an easy-to-use manual cell counting interface to public volunteers without a professional background. This interface can be opened by clicking the “Cell Counting” in the *Application Entry* view (step 1). The server can randomly pass back a randomly selected region in the image, and display it in the *Cell Counting* view (Fig. 6a). The end user can tap to place boxes as well as delete them. Fig. 6b is an example in which 9 cells are counted by gray boxes, and the sliders are provided for changing height and width of a selected box.

D. Capabilities of TissueWiki^{Mobile} on iPad

The current iPad app is developed with SDK version 3.2. Comparing to the iPhone, the much larger iPad touch screen size (9.7-inch) gives a clearer and more streamlined way to organize large amounts of information without losing its ease of use and scalability. Thus the development idea of TissueWiki^{Mobile} on iPad is merging different views and operations of the iPhone version into one integrative image browser (Fig. 7) instead of cycling through different views during the operation.

E. Annotation Knowledge Sharing

In addition to being stored in the local file system, created annotations can also be uploaded to the TissueWiki server so as to share the wealth of annotation knowledge. The upload operation can be performed when the user closes the image browsing and interface (Fig. 5c) in the iPhone version (step 9 in Fig. 3), or when the user clicks the “Upload” button in the

iPad version (button 10 in Fig. 7). Annotation information is encoded and transmitted to the central TissueWiki database using XML technology. Knowledge of each annotation is stored with correspondence to its creator's user name, creation date, and image ID, *etc.* Annotations can be accessed from TissueWiki via the discussion tab of the image detail page, as shown in Fig. 2.

Afterwards, users can retrieve the annotated images from the server for educational or collaborative purposes. Different professionals can have different insight on one image. Once the IHC image is requested from a TissueWiki^{Mobile} client, the server can transmit all of the created annotation versions to the client (step 8 in Fig. 3) so that the user can refer to expert annotation knowledge provided by others.

IV. System Performance

A. Usability Features of TissueWiki^{Mobile}

1) Mobility—Mobility is the key feature gained by using TissueWiki^{Mobile}. Users can connect to TissueWiki server and access medical knowledge via simple clicks anywhere through wireless connections without the constraint of being in front of computers.

2) Intuitive interface—Making the interface as intuitive as possible is the principle of tool design. It helps users easily understand the tool's operation the first time they encounter the design. The iPhone and iPad SDKs provide standard interface controls so that users feel familiar from other iPhone and iPad apps. Medical information is displayed systematically using navigation control and table views which are ideal for users to browse hierarchical data structures of antibody types, tissue categories, or clinical meta-data to find relevant histology images. Components in the TissueWiki^{Mobile} interface are labeled simply, but clearly, to avoid operation errors. For example, as shown in Fig. 7, the iPad version users can easily understand that the buttons labeled “Cancer” and “Breast” means the current image is affiliated with “breast cancer.” It is also prominent that these two buttons are used to evoke lists to select normal or cancer and one organ from the available tissue types.

3) Efficiency of use—TissueWiki automatically connects to the central database upon launch without requiring the user to type or look for the URL in bookmarks. The touch-sensitive screens of the iPhone and iPad provide a richer human computer interface using finger-operation that is often more efficient and more convenient than traditional tracking ball and touchpad mice. For example, in the iPhone version of TissueWiki^{Mobile}, users can use as few as 5 clicks to select one image from the entry view. When users are browsing images, they can easily perform two-finger zooming or one-finger panning on the high-resolution image instead of having scrollbars on the edges of windows.

The iPad-only popover view temporarily and unobtrusively displays additional information, controls, or choices related to buttons in the image browser. It provides a fast way to select antibody, cancer/normal tissue type, patient/image, and image mask, so as to quickly construct a search combination for a specific image (Fig. 8a and 8b). The popover view can also display metadata of the current image and its corresponding antibody and patient

information (Fig. 8c). It also furnishes a convenient way to view and edit contents of annotations without losing focus on images (Fig. 8d).

B. TissueWiki^{Mobile} Performance Assessment

A simple experiment was designed to measure and evaluate the usability features of TissueWiki^{Mobile}. Seven participants (5 students and 2 co-authors) from the Georgia Institute of Technology evaluated the performance improvement of database accessing using TissueWiki^{Mobile} on both the iPhone and iPad platforms. For the experiment, subjects were asked to performed four combinations of tasks including:

1. TissueWiki webpage via laptop computer
2. TissueWiki webpage via iPad Safari,
3. TissueWiki^{Mobile} on iPhone 3G, and
4. TissueWiki^{Mobile} on iPad.

In order to make the results comparable, we focused on portable devices. Performance with desktop computers and wired network connections were not evaluated. The USB mouse was not attached to the laptop computer for the same reason. IEEE802.11g Wi-Fi (as opposed to cellular) network connection was used for data communication between database and devices. Table II summarizes key hardware differences among the devices used in the experiment.

Prior to the tasks, subjects were familiarized with the background of TissueWiki, and the usage of the TissueWiki webpage and the TissueWiki^{Mobile} app on iPhone and iPad. Seven subtasks were performed in each actual task. One subtask was provided for practice in each task before the actual experiment. For each subtask, subjects were asked to find an IHC image following a given series of antibody, cancer or normal, and organ (*e.g.* CAB000064, Cancer, Lung). The image could be selected from anyone of the underlying patient/image list.

Performance was evaluated by timing the duration between the start of antibody searching and the time when the full-resolution image was displayed. All the influences-interface usability, hardware computing ability, *etc.*-were reflected in the duration. We believe these results accurately reflect the performance that an average user will experience with the tool.

C. Results and Discussions

According to Fig. 9, among the four tasks in the performance assessment experiment, the speed of database accessing was the fastest using the TissueWiki^{Mobile} iPad app. The efficiency was improved prominently by more than 50% compared with all other methods. Focusing only on the efficiency of TissueWiki webpage, there was no significant improvement using iPad Safari compared with the laptop computer. Although the TissueWiki^{Mobile} iPhone app only slightly improved the performance compared with the TissueWiki webpage on either laptop computer or iPad Safari, the maintained performance is still compelling after a dramatic reduction in screen size. Except for the two co-authors,

all of the five participants could learn the tool operation from a simple demo and were more satisfied with TissueWiki^{Mobile} apps than the TissueWiki website via Safari on iPad.

V. Conclusion and Future Works

In this paper, we have described a novel iPhone- and iPad-based bioinformatics tool, *TissueWiki^{Mobile}*, which connects users to a very large (~3TB) central digital repository for examining protein expression in tissues for the purpose of:

- extracting new knowledge using image processing,
- encouraging discussions about protein expression among experts, and
- storing expert knowledge in a shared environment to support discovery and dissemination of new ideas.

According to the results of the performance experiment, TissueWiki^{Mobile} prominently provides an easy to use interface and efficient data access ability on a mobile platform. This mobile platform allows users to access public, health-related tissue biopsy data whenever a wireless connection is available. Users can freely search for a certain antibody (i.e. protein target) and browse all of the corresponding images. Moreover, they can create annotations and paths for regions of interest via a portable iPhone and iPad using just a few clicks and avoid the inconvenience of being tied to a desktop computer. Afterwards, users can upload all of the annotation information as well as refer to expert knowledge provided by others to generate discussions on images.

TissueWiki^{Mobile} collaborates with TissueWiki and provides a paradigm for an integrated ubiquitous platform for medical data access and image browsing, satisfying different needs for clinicians, biomedical researchers, biomedical informaticians, and public volunteers.

A. Future Works

Our current work can be extended in several directions.

1) Efficiency of data search—It is not efficient to list all choices (e.g. more than 1,000 antibodies) at once for users to browse if they have a specific antibody of interested. Thus, there is a need to furnish a good categorization to organize such a complex knowledge, and provide a friendly interface to perform an advanced search and query.

2) Knowledge reusability—In order to improve the data management and make our image annotations and paths reusable in the entire cancer research community, we will adopt the model used by the caBIG Annotation and Image Markup (AIM) Project [13]. It has established a standard format that is semantically interpretable with the infrastructure of caBIGTM. Doing so can expand our project to support more widely used medical image standards, such as DICOM [24]. Therefore, with standard-formatted annotation content, images can be queried in a manner of Content-Based Image Retrieval (CBIR) which can improve accuracy and efficiency of image knowledge retrieving and analysis [25].

3) Data extensibility—Currently the data source of TissueWiki^{Mobile} is antibody profiling information based on IHC images from the HPA project. However, other data types available on TissueWiki include staining to detect tumor margins and Quantum Dot Antibody-conjugate stains.

4) Educational platform—We hope to make a bigger impact by deploying the TissueWiki^{Mobile} to the Apple App Store for general use by iPhone and iPad users. We believe that volunteers can provide valuable human data interpretation power to accomplish simple tasks like counting cells and learn a great deal about pathology and histology in the process so as to increase the popularity of the tool and provide a participatory educational platform.

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Figure 1. TissueWiki web site front page

Figure 2. Architecture of the TissueWiki and TissueWikiMobile prototypes

Figure 3. Workflow of the iPhone app's operation (numbers) and interface views (blue boxes)

Figure 4. TissueWiki^{Mobile} interface corresponding to Fig. 3 - part 1: (a) Application Entry, (b) Antibody List, (c) Antibody Detail, (d) Antibody Information, the view of Gene/Protein Information of antibody meta-data, (e) Cancer/Normal List, the figure shows the list for cancer tissue selection, and (f) Patient List.

Figure 5.

TissueWikiMobile interface corresponding to Fig. 3 - part 2: (a) Image/Patient Detail, (b) the detailed image meta-data, (c) Image Browser, (d) Image Browser showing one annotation and one path, (e) zooming and panning result of (d), and (f) Annotation Form, a form to fill for the selected annotation.

(a)

(b)

Figure 6. Cell counting interface

Figure 7.

An integrative image browsing interface of TissueWiki^{Mobile} on iPad. The interface consists of buttons with different functionalities including (1) antibody selection, (2) normal or cancer selection, (3) tissue type selection, and (4) patient/image selection, (5) mask selection, (6) antibody, patient, and image metadata browsing, (7) annotation hide/show switch, (8) annotation color selection, (9) annotation creation (left), path creation (middle), and zooming and panning (right), and (10) annotation upload.

Figure 8. Popover views of TissueWiki^{Mobile} iPad version. (a) A list of cancer/normal tissue type selection. The figure shows the list for cancer tissues. (b) Patient list view. (c) Antibody, patient, and image metadata view. The figure shows the antibody metadata. (d) Annotation form. It is provided to view and fill the annotation's content.

Figure 9. Speeds of database accessing via TissueWiki webpage using laptop and iPad, and TissueWiki^{Mobile} on iPhone and iPad

TABLE I
MOBILE MEDICAL KNOWLEDGE RETRIEVAL APPLICATIONS

Name	Purpose	Cost
OsiriX [4]	Annotation of Radiology Images (stored in PACS)	\$20
mobileLexE VS [5]	Access Medical Terminologies	N/A
caBIO [6]	Browse the Cancer Bioinformatics Infrastructure Objects database	free
Epocrates (Light) [7]	Detection of drug interactions and helpful calculations	free
BioGene [8]	Gene function information search	free

TABLE II
HARDWARE SPECIFICATIONS OF DEVICES USED IN THE PERFORMANCE
ASSESSMENT EXPERIMENT

Device	Laptop Computer	iPad	iPhone 3G
Processor	1.83 GHz	1 GHz	620 MHz
RAM	2GB DDR2	256 MB DRAM	128 MB DRAM
Screen Size	14.1"	9.7"	3.5"
Screen Area	95.43 in ²	45.16 in ²	5.88 in ²
Screen Resolution	1024 × 768	1024 × 768	360 × 480