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Design and Evaluation of Cervical Pap Smear E-learning System for the Education of Cytopathology

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Abstract: Cytology evaluation is a safe, efficient, and well-established technique for the diagnoses of many diseases. Its ability to reduce the mortality and morbidity of cervical cancer is through mass screening to early detect dysplasia or pre-invasive cancer cells. Classical cytological diagnosis is based on microscopic observation of specialized cells and qualitative assessment using descriptive criteria, which may be inconsistent because of subjective variability of different observers. Recently, web-based learning is becoming prevalent in schools and enterprises around the world for its advantages of providing easy access to information and knowledge, supporting ubiquitous learning environment, and increasing cost-effectiveness for both educational institution and students. The objectives of this study were to design automatic classifiers based on integrated genetic algorithm (GA) and support vector machine (SVM) to cluster four different types of cervical cells and to discriminate dysplasia from normal cells, as well as to implement a web-based cytopathology training and testing system to increase learning efficiency of cytopathologic education. A prototypic system composed of a microscope, digital camera, personal computer, cellular processing and analyzing program, and cell classifier was designed to facilitate acquisition, image processing and analysis, and classification of cell images. Furthermore, a web-based cytopathology training and testing (WBCTT) systems were developed based on the classified cell images to train students, resident physicians, and novice pathologists to discriminate various types of cervical cells. The experimental results demonstrate that the classification and diagnostic accuracy achieves 96.82% and 99.6% , respectively. System evaluation based on questionnaire survey of extended technology acceptance model (TAM) shows that the proposed system embedded with cell classifier and WBCTT is useful in cytopathology diagnosis and training. Most of the users agreed the operation interface is friendly and easy to use. They also expressed strong behaviour intention to further adopt the system. It is expected to have significant contributions in increasing diagnostic efficiency and promoting learning efficiency.

Keywords: Cytopathology, Genetic Algorithm, Support Vector Machine, Classifier, E-Learning, Technology Acceptance Model.

1 Introduction

Cytology evaluation is a safe, efficient and well-established technique for the diagnoses of many diseases. The most famous success in cytology is its ability to reduce the mortality and morbidity of cervical cancer through mass screening. One role of cytology is directed to early detection of dysplasia or pre-invasive cancer cells. Once the abnormal cells are detected, the patient can be scheduled for a biopsy examination and subsequent surgical treatments. Consequently, the progression of the cancer can be stopped at an early stage.

Classical cytological diagnosis is based on microscopic observation of specialized cells and qualitative assessment using descriptive criteria, which may be inconsistent because of subjective variability of different observers [1]. To lower the false negative rate in screening, many advanced technologies involving sampling, smear preparation, or screening quality control

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have recently been developed and introduced [2]. Commercial devices that use these technologies can be divided into the following categories based on their approaches: (1) improved slide preparation to reduce sampling error, for example thin-layered liquid-based preparation (ThinPrep, SurePath, Tripath) [3]; (2) reduced workload and screening error as in the autoscreening system (ThinPrep Imaging System, Cytyc, Boxborough, MA; and FocalPoint System, Tripath Imaging, Burlington, NC); (3) improved laboratory quality control like rescreening (Papnet) [4]; and (4) enhanced quality assurance, such as the proficiency test [5]. However, most of these devices do not assist objective diagnosis by providing the calculable parameters that would eliminate interpretation errors and inter-observer discrepancy [6]. In addition, they are not applicable to the general cytological laboratory because of high cost and technical or linguistic gaps [7,8]. Thus, without a reproducible and quantitative tool, observer bias is still an unsolved problem in the routine cytological laboratory. Diagnostic divergence caused by visual observation remains.

Computerized Cell Classification System The technique of computerized image analysis used to assist artificial diagnosis of cell abnormalities or tumors in cytopathology or histopathology also can provide accurate and objective evaluation of nuclear morphology. Quantitative methods for estimating a cytological specimen can be traced back some 30 years and are still continuing to develop [4,9,10,11,12,13,14,15] Reliability, accessibility, cost, efficiency, technical maintenance, and linguistic communication are considerations that need to be taken into account in any new design. Due to revolution and evolution of new technologies, enhanced computational power of computation, decreased cost of hardware and software, and the prevalence of the Internet, more and more systems being developed use computational algorithms for cellular image analysis [16,17,18] Such approaches promise to resolve the limitation of subjective analysis, especially in the fields of bioinformatics, biology, and medicine.

Medical Education in Cytopathology Web-based learning is becoming prevalent in schools and enterprise around the world for its advantages of providing easy access to information and knowledge, supporting ubiquitous learning environment, and increasing cost-effectiveness for both educational institution and students. A recent investigation in Taiwan showed that more than 90% of public health nurses expressed strong behavior intentions in web-based learning to capture new knowledge to elevate the quality of care [19]. Online telepathology was reported to be a useful technique in providing continuous education for pathologists to view microscopic images through the Internet [20,21]. Kalinski et al [22] proposed a virtual 3-D specimen system for online pathology education by taking advantage of JPEG2000 Internet protocol.

Virtual microscopy is becoming popular for pathologists to view microscopic images online. A digital slide system for online browsing on the Internet is generally composed of 3 components, including digital slide acquisition to acquire the slide images, image server to store images and make images available on the web, and client browser to support users browsing the digital slide images [23]. However, there are still several drawbacks needed to be improved, such as (1) setting up a system is expensive, (2) needing huge memory storage for saving scanned slides, and (3) spending a lot of time to scan a slide [24]. Another motivation of this investigation is that although the streaming technology is available, the network bandwidth needed for receiving a whole-slide image is significantly higher than an individual cell image with much smaller memory size. Hence, a cheaper online training system based on images acquired using general microscope accompanied with a high-resolution digital camera is still needed.

The structure of this paper is organized as follows. Section 2 presents the Computerized Cellular Image Analysis and Classification System. The Web-Based Cytopathological Training and Testing System and System Evaluation are described in Sections 3 and 4, respectively. Finally, brief Discussions and Conclusions are made in Section 5.

2 Computerized Cellular Image Analysis and Classification System

In our previous study, we set up a reproducible and reliable analytical tool to facilitate interpretation and to create a reliable database [25]. All the analysis and experiments were done based on developed software programs and the equipment in a routine cytological laboratory. The system consists of a microscope, digital camera, personal computer, semi-automated cellular processing and analyzing programs, and SVM classifiers. The system architecture is illustrated in Figure 1.

The procedure is divided into the following steps: acquisition and categorization of cell images, image editing and processing, contour segmentation using random walks [26] measurement and analysis of cellular morphology and texture, classification of cell types using SVM, and system assessment with TAM. Customized programs were designed in our laboratory to simplify the analytic procedures facilitate cellular image review, organize the cell images, and calculate the morphmetric features of cells.

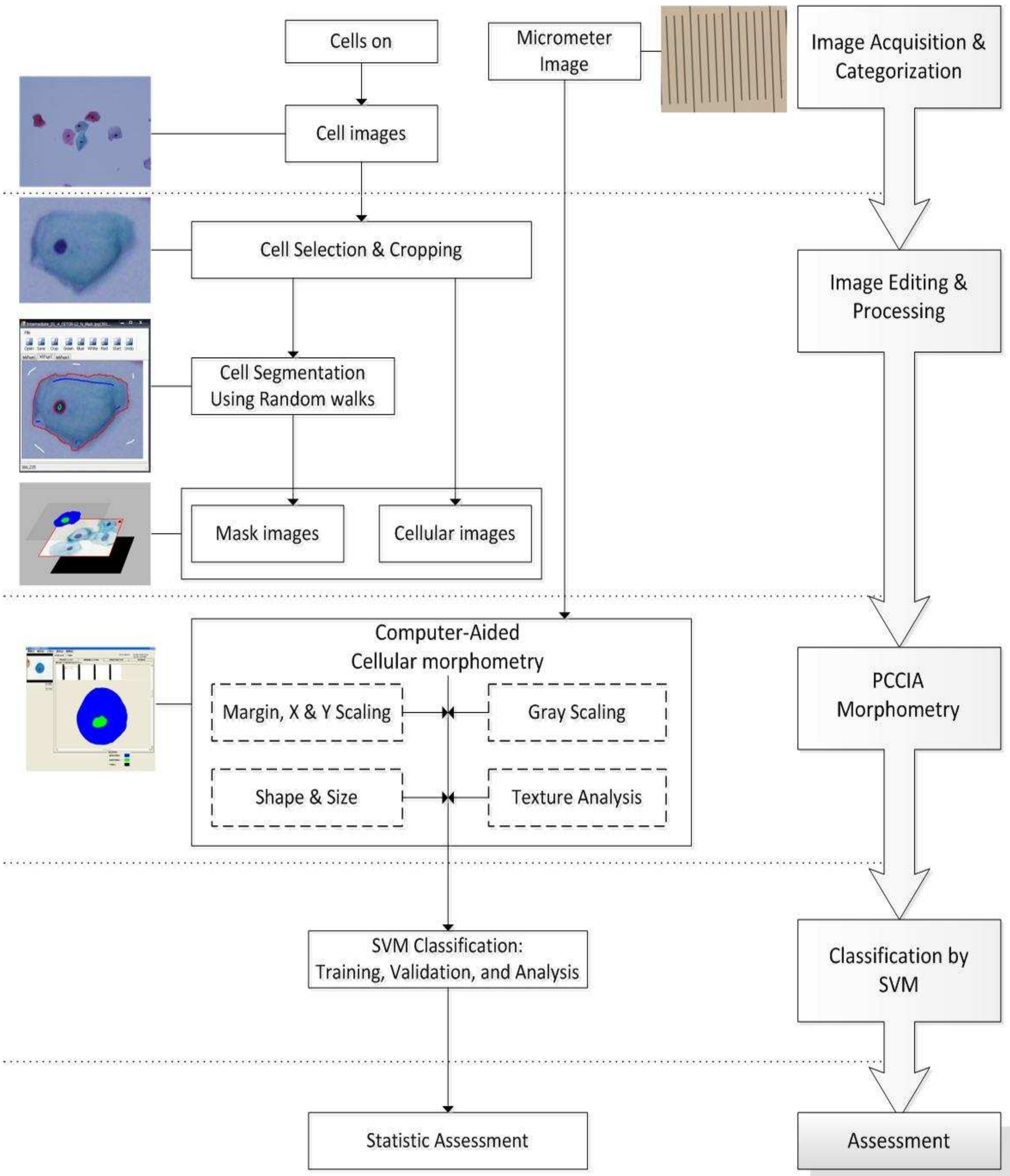


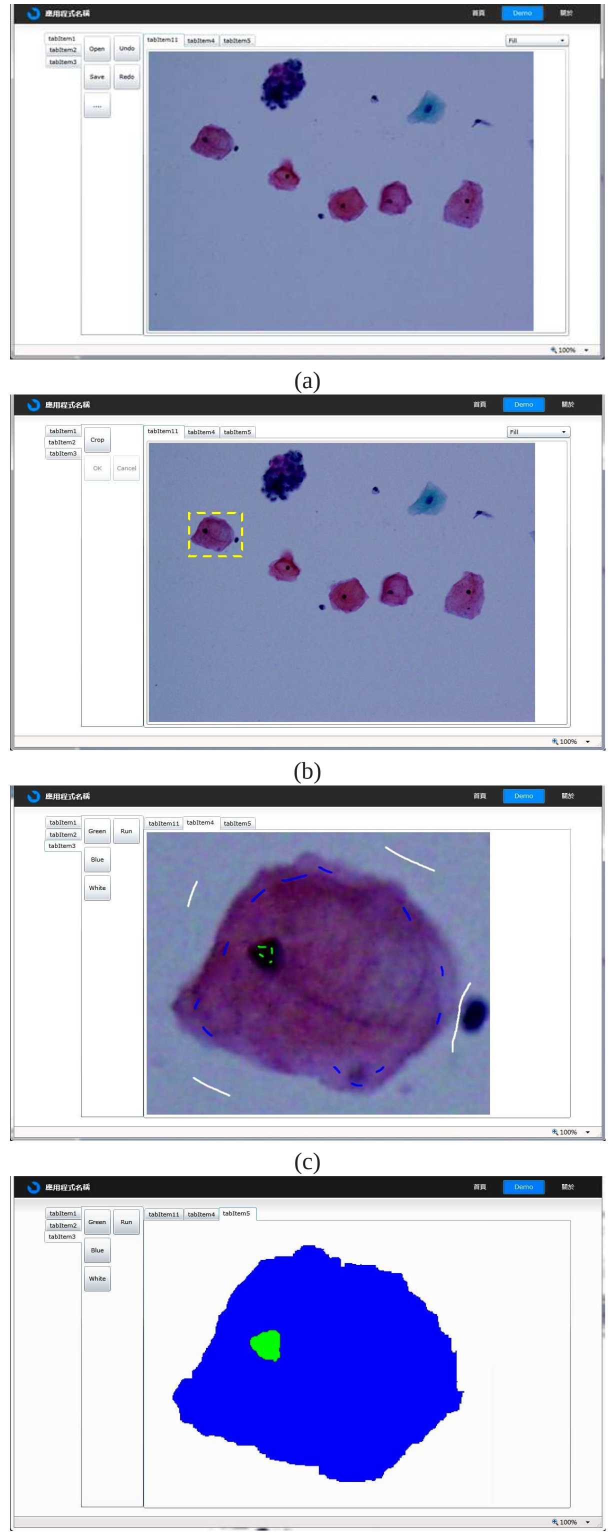
Fig. 1: System architecture of the computerized cellular image analysis and classification system.

Acquisition and categorization of cell images Cytological images were captured using a high-resolution digital camera (Olympus C-5060, Japan) mounted on a microscope (Olympus BX 51, Japan) and stored as digital format Cell images can be captured with 3 different scales of magnification (100x, 200x and 400x) and inspected easily in 3 magnifications simultaneously. All the images can be renamed using a scheme based on cell type, standardized sequence number, magnification, requesting pathological number, and diagnostic code for easy documentation and retrieval by the analysis program and SVM classifier.

Image editing and processing Extraction of individual cellular images and generation of their corresponding nucleus and cytoplasm masks were obtained using a program designed based on random walk algorithm [26]. First, the program automatically adjusts the color of the image on the computer to a visual view very similar to the view using the microscope. Secondly, individual cells can be selected with the cropping tool, followed by the segmentation of nucleus and cytoplasm with random walk algorithm.

Figure 2 shows the web-based cell image editing and processing module to provide functions of online image editing and processing. Figure 2(a) shows the function of opening and browsing cell images. The pathologist first selects and crops the interested cells from a scanned slide image, Fig. 2(b), followed by delineating approximately representative background (white), cytoplasm (blue), and nucleus (green) regions using the designated tools, Fig. 2(c). Then, the contours of cytoplasm and nucleus were automatically detected, Fig. 2(d). If the user is not satisfied with the detected contours, the representative regions can be re-marked to shrink or expand the contours. An extracted cell image and its masks are saved as two different but associated files, which will be used to calculate morphological features of the cytoplasm and nucleus by an automated analysis program for the recognition of different cell types, as detailed in the following section.

Measurement and analysis of cellular morphology and texture A software program, namely Personal Computer Based Cellular Image Analysis (PCCIA) system, was designed to perform the cellular image analysis. PCCIA can automatically measure the morphometric parameters of the cells either individually or in a batch. With the help of internal calibration using the micrometer image, various parameters were obtained for the evaluation of the nuclear size and shape irregularity of a cell These parameters include nuclear perimeter, area, maximum length, maximum width, ratio of nucleus and cytoplasm areas (N/C ratio), maximum length from axel center to perimeter (MAP), average length from axel center to perimeter (AAP), maximum length from center of gravity to perimeter (MGP), and average length from center of gravity to perimeter (AGP).



(a) (b) (c) (d)

Fig. 2: (a) Web-based cell image editing and processing module for (a) file open and slide view, (b) cell cropping, (c) contour detection using random walk algorithm, and (d) mask generation..

Other parameters, including entropy of the co-occurrence matrix (ECM), contrast of the co-occurrence matrix (CCM), coarseness and contrast of Tamura features were also applied to analyze textural features of the nuclei. A co-occurrence matrix C is a two dimensional $n \times n$ matrix obtained from image I where the element in location (i, j) is the number of occurrences that the pixel value i in image I has a pixel value j in its neighborhood with a relative distance d. The entropy and contrast of an image can be calculated from the co-occurrence matrix from the following equations.

$$Entropy = -\sum_i \sum_j P(i, j) \log P(i, j) \tag{1}$$

$$Contrast = \sum_i \sum_j (i - j)^2 P(i, j) \tag{2}$$

where $P(i, j)$ indicates the probability of a pixel with gray-level i having a pixel with gray-level j adjacent to it.

Tamura features, including coarseness, contrast, directionality, linelikeness, regularity, and roughness, are widely adopted for characterizing low-level statistical properties of texture [27]. In this study, coarseness and contrast were selected for describing the texture within the cell nucleus.

Classification of different cell types Genetic algorithm (GA) and support vector machine (SVM) were integrated for selecting features, fine-tuning SVM parameters, and constructing decision support classifiers in a single system. The goal of SVM is to separate multiple clusters with a set of unique hyperplanes that have the greatest margins to the edge of each cluster. Hyperplanes that separate two clusters is not unique for other linear classifiers. For a two-class classification example, the hyperplane separating two classes that leaves the maximum margins from both classes [28, 29]. For a nonlinear classifier, various kernels including polynomial, radial basics function, and hyperbolic tangent can be used for mapping the original sample space into a new Euclidian space. The linear classifier can then be designed for classification.

It is believed that SVM is superior to traditional statistical and neural network classifiers. However, it is critical to determine suitable combination of SVM parameters (C and γ) to achieve better classification performance. GA can find optimal solution within an acceptable time, and is faster than dynamic programming using exhaustive searching strategy. By taking the advantage of GA in quickly searching the optimal features and SVM parameters, a nonlinear hyperplane with greatest margin can be obtained by using SVM to classify two clusters. Classification of multiple clusters can be easily expanded. The freeware LIBSVM [30], a library for SVM, was adopted to design the SVM classifier. The GA was modified to combined with the LIBSVM to achieve the objective of designing effective classifiers.

Figure 3(b) shows the model which combines GA and SVM for the construction of classifiers to classify 4 different cell types and to discriminate dysplasia from normal cells. As depicted in Fig. 3(a), the chromosome of the GA is consisted of SVM parameters and features extracted from collected data. The fitness value is the accuracy of SVM classification of an individual iteration. After several iterations, the best solution with optimal SVM parameters and selected features can be obtained for classifier construction.

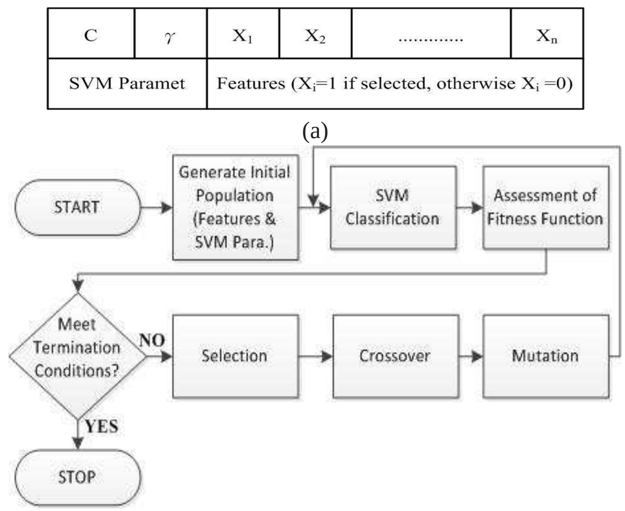


Fig. 3: (a) Chromosome and (b) flowchart of the proposed method with genetic algorithm applied for determining features and adjusting SVM parameters, while SVM used for classification of data and calculation of fitness values.

Table 1 compares the classification accuracy and diagnostic performance between integrated GA and SVM and traditional SVM classifiers. The results show that integrated GA and SVM classifiers outperforms traditional SVM classifiers [25] in discriminating 4 different types of cervical cells (96.82%) and diagnosing dysplasia cells (99.6%). The high classification accuracy is promising in facilitating classification of cell images to be included in the question bank with good quality, which in turn can be used for the education of cytopathology.

3 Web-Based Cytopathological Training and Testing System

After automatic discrimination of cell type by the classifier followed by visual verification by experienced pathologists, the cell can be added to the question bank A web-based cytopathological training and testing (WBCTT) system was designed to train students, resident

Table 1: Comparisons of classification and diagnostic performance of integrated GA & SVM and SVM classifiers

Cell Type	GA+SVM	SVM [25]
Superficial (N=139)	94.24% (131/139)	96.40% (134/139)
Intermediate (N=178)	98.88% (176/178)	91.57% (163/178)
Parabasal (N=128)	97.66% (125/128)	93.75% (120/128)
Dysplastic (N=58)	94.83% (55/58)	100% (58/58)
All cells (N=503)	96.82% (487/503)	94.43% (475/503)
Normal (N=445)	99.55% (443/445)	98.4% (438/445)
Dysplasia (N=58)	100% (58/58)	100% (58/58)
All Cells (N=503)	99.6% (501/503)	98.6% (496/503)

physicians, and novice pathologists how to discriminate different types of cervical cells by using the cells stored in the question bank. Figure 4 depicts functions and operations of the WBCTT system which integrates PCCIA system, cell classifier, and web management. The WBCTT module supports functions including question bank management, test management, and online testing operation. Figure 4(a) shows the welcome page of the WBCTT. The question bank management is demonstrated in Fig. 4(b). Figures 4(c) and (d) illustrate the operations of test management and creation of a new test, respectively.

With the assistance of PCCIA and cell classifier, the types of cells on a newly scanned pap-smear image can be quickly and easily discriminated, which are then added and stored in the question bank. With regard to the testing management, the instructor can design a test by selecting questions in question bank by determining the number of questions as well as the numbers of individual cell types. The system supports 3 ways in designing tests, i.e. random assignment, and question assignment based on cell types and categories of pathologic diagnosis.

Development Environment and Tools A high-performance personal computer installed with Windows Server 2003 R2 operating system is used as the server to house question banks and relevant software programs. Additionally, Microsoft Internet Information Services 6 (IIS6) and Microsoft SQL Express 2008 R2 Express were also installed to serve as web server and database management system, respectively. Microsoft Visual Studio 2010 and ASP.net 4.0 (C#) were used to design dynamic web pages.

The operating system of the client site workstation can either be Windows XP or Windows 7 with Internet Explorer 8 or FireFox 3 installed. The recommended hardware specification is as follows: (1) CPU- 1 GHz or higher; (2) RAM- 1GB or higher; (3) Screen resolution- 1024 * 768 or higher.

Preparation of Questions Although the classification results using nucleus feature achieved satisfactory accuracy, verification and manually re-classification need to be done by experienced pathologists to accomplish

Fig. 4: Web-based cytopathological training and testing system. (a) Welcome page, (b) question bank management, (c) test management, and (d) creation of a new test.

100% accuracy. Nonetheless, the cell classifier is able to save a lot of time and is useful in providing valuable suggestion for the pathologist to make final decision in cell classification. The classified cervical cells were then added and saved in the question bank for further pathology education.

4 System Evaluation

The online training and testing system was used for training cytopathologists and cytotechnicians to discriminate different types of cervical cells. It also serves as a platform for pathologists to exchange their experience or to seek help regarding the cases which are difficult to resolve. A questionnaire designed based on the modified technology acceptance model (TAM) [31] was used to evaluate perceived usefulness (PU), perceived ease of use (PEU), and behavior intention (BI) of the web-based e-learning system. In addition to the 3 constructs proposed by Davis [32] 4 additional constructs, including computer self efficacy (CSE), technical support and training (TST), information quality and integration (IQI), and Information Privacy (IP), were also adopted to verify the model [33].

Pathologists and technicians were recruited from hospitals located in middle Taiwan. A total of 93 persons, including 17 cytopathologists, 73 cytopathological technicians, and 3 other professionals whose tasks related to pathology, were recruited for evaluating PEU, PU, and BI of the web-based e-learning system. After a short tutorial of describing the rules for discriminating different types of cervical cells, the users were asked to operate the system, do online tests and finally fill the questionnaire following the learning and testing.

As shown in Table 2, the values of Cronbach's alpha for 7 constructs are all greater than 0.8, indicating great reliability of the questionnaire. Descriptive (mean and standard deviation) and inferential (one sample t-test) analyses of the constructs of the extended TAM are also shown in Table 2. As indicated in this table, the scores of all the 7 constructs are significantly greater than the neutral value (3) with a level of 0.001 (one sample t-test,) based on a 5-point Likert scale. As illustrated in Figure 5, the structure equation modeling (SEM) analysis of the extended TAM shows that PU and PEU affect BI of system adoption with a significant level of 0.001 In addition, CSE influences the PEU ($p < 0.001$) and IQI affects both PEU ($p < 0.01$) and PU ($p < 0.001$) Information privacy doesn't affect either PU or BI.

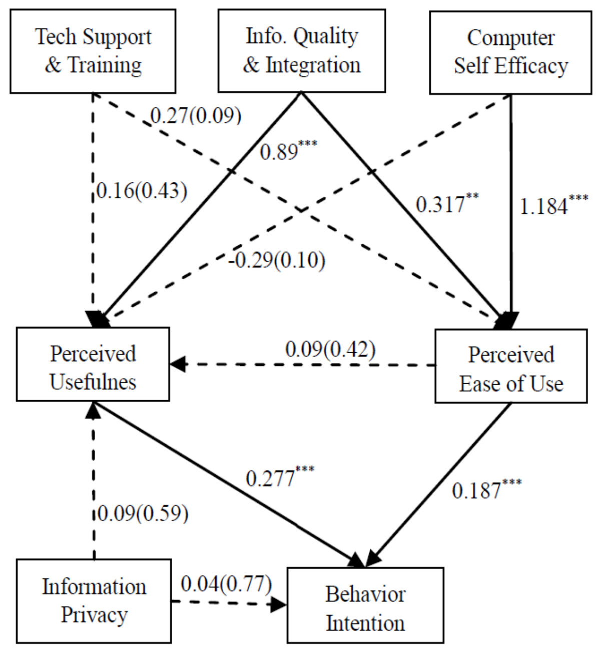
5 Discussions and Conclusions

TAM is a model widely used in assessing an information system or information technology. In general PU and PEU have direct affect on BI, while PEU has positive effect on PU [32] The results of the present study indicate that PU and PEU significantly affect behavior intention of users to adopt the proposed cell classification and training system, which is consistent to the TAM [32]. Unfortunately, PEU doesn't demonstrate positive effect on PU in this study

The effects of TST on the PU and PEU are not supported either, which is consistent to previous investigations with regards to mobile computing acceptance on healthcare industry [34] and personal computing acceptance in small firms [35] The reason might be that web-based information systems are becoming popular and most of them are designed with unified graphic user interface. The information system

Table 2: Reliability and descriptive and inferential analyses of TAM questionnaire survey. ***Significance with p <0/001.

Construct (N=93)	Mean	STD	Cronbach's Alpha
Behavior Intention***	3.48	.67	.865
Perceived Usefulness***	3.35	.88	.879
Perceived Ease of Use***	3.77	.82	.852
Computer Self Efficacy***	3.95	.55	.884
Tech Support and Training***	3.55	0.59	.867
Info Quality & Integration***	3.57	.77	.854
Information Privacy***	3.68	.64	.886



(a)

Fig. 5: Experimental results of the structural model. Note: *Path is significant with p <0.05; **Path is significant with p <0.01; ***Path is significant with p <0.001.

proposed here was developed and executed under Microsoft environment with friendly interface, enabling the users very easy to operate. It is observed that most users can operate the system intuitively without training which is also manifested by the high survey score (3.95±0.55) of the CSE construct. Most of the recruited users reported themselves as skillful computer users. In addition, CSE has strong impact on PEU ($p < 0.001$).

It can be found that CSE has strong effect on PEU ($p < 0.001$) but not on PU which is only partially coincident to the survey of mobile computing acceptance on healthcare industry. In [34], it was reported that CSE affects both PEU and PU Tung and Chang [36] reported that CSE has a positive effect on behavior intention to use the online course material for nursing students. In this study, CSE indirectly affects the behavior intention of the cytopathologists and cytotechicians to adopt the proposed system through PEU.

Information quality and system integration were reported to be two important factors which highly influences PU and post adoption of an information system [37]. In addition to PU ($p < 0.001$), IQI has also been shown to have significant influence on PEU ($p < 0.01$) in our study. The users were satisfied with the information quality and system integration (3.57±0.77) of the proposed system, which in turn increased the BI of adopting the system.

In conclusion, in this study a prototypic system composed of a microscope, digital camera, personal computer, cellular processing and analyzing program, and cell classifier has been designed for cell image processing and analysis, and automatic cell discrimination. High performance in discrimination of different cervical cells and diagnosis of dysplasia cells was achieved by a multiple-class and 2-class classifiers designed based on an integration of genetic algorithm (GA) and support vector machine (SVM) In addition, a web-based cytopathology training and testing (WBCTT) system was developed to train students, resident physicians, and novice pathologists to discriminate various types of cervical cells. After careful verification, the classified cells can be added to the question bank to provide training and testing materials for efficient cytopathology education System evaluation based on extended technology acceptance model (TAM) shows that the proposed system is useful in diagnosis of dysplasia cells and education of cytopathology by providing friendly and easy-to-use interface. The users expressed strong behavior intention to further adopt the system.

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