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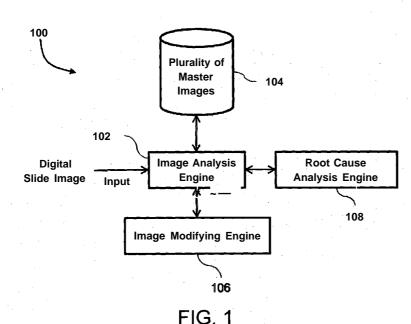
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(54) Title: METHOD AND SYSTEM FOR PROCESSING A DIGITAL SLIDE IMAGE OF A STAINED TISSUE



(57) Abstract: The invention provides a method and system for processing a digital slide image of a stained tissue. The method in cludes receiving the digital slide image for processing and comparing the digital slide image with a master slide image to determine if the digital slide image is of an acceptable quality. The method includes comparing each parameter of a set of parameters of the digital slide image with a threshold value to determine if the digital slide image is of the acceptable quality. After determining that the digital slide image is of the acceptable quality, the digital slide image is modified. One or more characteristics of the digital slide image are modified based on the comparison of the digital slide image with the master slide image. If the digital slide image is not of the acceptable quality, a cause of error is identified by utilizing root cause analysis information.

METHOD AND SYSTEM FOR PROCESSING A DIGITAL SLIDE IMAGE OF A STAINED TISSUE

FIELD OF THE INVENTION

[0001] The invention generally relates to the field of processing a digital image. More specifically, the invention relates to a method and system for processing a digital slide image of a stained tissue.

BACKGROUND OF THE INVENTION

[0002] Generally, stained tissue is used to makes morphological interpretation in a histology laboratory. In modern histology, digital slide images of the stained tissue are used for the morphological interpretation. An improperly stained tissue and improper digital slide image makes morphological interpretation difficult in a histology laboratory. Various factors affect the quality of a digital slide image of a stained tissue. The factors can be one or more of, but is not limited to, staining techniques, chemical manufacturers, consistency in staining procedures, scanning conditions, staining machines, and expertise of personnel involved. Therefore, quite often, histology faces problems of inconsistencies associated with the one or more factors mentioned above during slide processing. For example, there could be variations associated with staining machines, this could be due to variation in exposure time, improper tissue processing or improper slicing. The inconsistency in staining can include under staining or over staining of the tissue.

[0003] The variations can be controlled by optimizing the protocol of generating a digital slide image by implementing tighter controls. However, there are different optimized protocols from place to place and machine to machine which can lead to variation in the quality of the digital slide image. Further, preferences of doctors add to variations in the quality of the digital slide image. The variation in the quality of a digital slide image of a stained tissue can be reduced using optimized protocols. However, the variation in the quality cannot be completely eliminated using optimized protocols.

[0004] In light of the above, there is a need for an improved method and system for obtaining a standard quality of digital slide images of stained tissues.

BRIEF DESCRIPTION OF FIGURES

[0005] The accompanying figures, where like reference numerals refer to identical or functionally similar elements throughout the separate views and which together with the detailed description below are incorporated in and form part of the specification, serve to further illustrate various embodiments and to explain various principles and advantages all in accordance with the invention.

[0006] FIG. 1 illustrates a block diagram of a system for processing a digital slide image of a stained tissue in accordance with an embodiment of the invention.

[0007] FIG. 2 shows a graphical representation of image classes.

[0008] FIG. 3 illustrates a fish bone diagram to represent the staining variations.

[0009] FIG. 4 illustrates modules of the root cause analysis engine in accordance with an embodiment of the invention.

[0010] FIG. 5 illustrates a graph representing staining variation classes with deviation of 20% from the master slide image.

[0011] FIG. 6 shows a sample plot of master liver image red, green, blue channel histogram values varied from 0 to 255.

[0012] FIG. 7 shows a template of an error report generated for images classified as under or over images.

[0013] FIG. 8 illustrates a flow diagram of a method for processing a digital slide image of a stained tissue in accordance with an embodiment of the invention.

[0014] FIG. 9 illustrates a flow diagram of comparing a discarded or rejected digital slide image with the master slide image at run time in accordance with an embodiment of the invention.

[0015] FIG. 10 illustrates a flow diagram of a method for verifying if an appropriate identifier is associated with a digital slide image.

[0016] FIG. 11 depicts examples of digital slide images which shows staining variation absorbed in a laboratory data.

[0017] FIG. 12 depicts digital slide images corrected using the system in accordance with an embodiment of the invention.

[0018] FIG. 13 illustrates a probable set of master slide images created by staining in ideal environment conditions and varying staining time by (+/-) 10% and 20% from the standard staining time.

[0019] FIG. 14 depicts a temporary master slide image.

[0020] FIG. 15 illustrates functionality of a Root Cause Analysis (RCA) configuration tool.

[0021] FIG. 16 illustrates functionality of an imagesmart configuration tool.

[0022] FIG. 17 illustrates functionality of an imagesmart configuration tool

[0023] FIG. 18 depicts a liver master image.

[0024] FIG. 19 depicts a test image of a digital slide image which is classified into a normal image class.

[0025] FIG. 20 depicts a converted test image.

[0026] FIG. 21 depicts a test image of a digital slide image which is classified into an under image class.

[0027] FIG. 22 depicts a test image of a digital slide image which is classified into an over image class.

[0028] FIG. 23 depicts a test image which is classified as a high artifacts image.

[0029] FIG. 24 depicts a test image which is classified as a high out of focus image.

[0030] Skilled artisans will appreciate that elements in the figures are illustrated for simplicity and clarity and have not necessarily been drawn to scale. For example, the dimensions of some of the elements in the figures may be exaggerated relative to other elements to help to improve understanding of embodiments of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0031] Before describing in detail embodiments that are in accordance with the invention, it should be observed that the embodiments reside primarily in method steps and system components related to processing a digital slide image of a stained tissue.

[0032] In this document, relational terms such as first and second, top and bottom, and the like may be used solely to distinguish one entity or action from another entity or action without necessarily requiring or implying any actual such relationship or order between such entities or actions. The terms "comprises," "comprising," or any other variation thereof, are intended to cover a non-exclusive inclusion, such that a process, method, article or composition that comprises a list of elements does not include only those elements but may include other elements not expressly listed or inherent to such process, method, article or composition. An element proceeded by "comprises ...a" does not, without more constraints, preclude the existence of additional identical elements in the process, method, article or composition that comprises the element.

[0033] Generally speaking, pursuant to various embodiments, the invention provides a method and system for processing a digital slide image of a stained tissue. The method includes receiving the digital slide image for processing and comparing the digital slide image with a master slide image to determine if the digital slide image is of an acceptable

quality. The method includes comparing each parameter of a set of parameters of the digital slide image with a threshold value to determine if the digital slide image is of the acceptable quality. After determining that the digital slide image is of the acceptable quality, the digital slide image is modified. During the modification, one or more characteristics of the digital slide image are modified based on the comparison of the digital slide image with the master slide image. If the digital slide image is not of the acceptable quality, a cause of error is identified by utilizing root cause analysis information. Though the method and system describes digital slide image of the stained tissue, the method and system can be applied to other medical images.

[0034] FIG. 1 illustrates a block diagram of a system 100 for processing a digital slide image of a stained tissue in accordance with an embodiment of the invention. System 100 includes an image analysis engine 102, a database of master images 104, an image modifying engine 106 and a root cause analysis engine 108.

[0035] A slide of a stained tissue can be prepared manually or by a staining machine. A digital slide image of the stained tissue can be generated using an image capturing device which includes a microscope and a scanner. Once the digital slide image is generated, the digital slide image is provided as an input to system 100. The stained tissue can be obtained by using one or more stains such as, but not limited to, a H&E stain, a Masson's Trichrome stain, a modified Grocott's Methenamine Silver (GMS) silver stain, a Periodic Acid Schiff (PAS), a Perls' Prussian Blue, a Ziehl Neelsen, an Alcian blue, a Gomori Trichrome (blue), a Mucicarmine, a Congo red, a Cresyl Violet Stain, a Luxol Fast Blue (MBS) Stain, an Alizarin Red S Stain, a Perls' Prussian Blue Stain, a Giemsa Stain, an Oil-Red-O, a Phloxine-B, Sudan Black, a Toluidine Blue Stain and a Von Kossa.

[0036] Image analysis engine 102 is configured to receive the digital slide image of the stained tissue. In an embodiment, image analysis engine 102 is also configured to receive a plurality of digital slide images. For example, a batch of 500 to 1000 digital slide images of liver tissue stained using H&E stain can be received as an input by image analysis engine 102.

[0037] Image analysis engine 102 is also configured to compare the digital slide image with a master slide image to determine if the digital slide image is of an acceptable quality. A digital slide image is of an acceptable quality when there is a scope to modify one or more characteristics of the digital slide image to obtain an enhanced digital slide image. Upon receiving a digital slide image, image analysis engine 102 is configured to determine an identifier associated with the digital slide image. An identifier is used to determine a type of tissue associated with a digital slide image. The type of the tissue can be one of, but is not limited to, liver, muscle, uterus, heart, fat tissue, gastrointestinal tissue, lung, renal, stomach, skin, thyroid, lymph node, bone, pancreas, spleen, eye, ovary, and central nervous system. Image analysis engine 102 is configured to verify the association between the type of tissue and the digital slide image by analyzing the digital slide image. Image analysis engine 102 is also configured to automatically determine the type of tissue in the digital slide image for verifying if an appropriate identifier is used.

[0038] Further, image analysis engine 102 is configured to select a master slide image from plurality of master images 104 based on the identifier associated with the digital slide image. Each master slide image in plurality of master slide images 104 is specific to a type of tissue. For example, a master slide image can be specific to a liver tissue. Additionally, a master slide image can be specific to a type of tissue and a specific stain. For example, a master image can be specific to liver tissue stained using H&E stain. Further, plurality of master slide images 104 can be specific to a laboratory.

[0039] In an embodiment, the plurality of master slide images for the laboratory can be created by associating each master slide image with a type of tissue. Each master slide image is associated with a type of tissue by collecting a plurality of digital slide images for the type of tissue. The plurality of digital slide images is ranked based on predetermined criteria. A digital slide image of the plurality of the digital slide image is selected as the master slide image for the type of tissue based on the ranking.

[0040] Consider an exemplary embodiment of associating a master slide image with a type of tissue. Tissue slides of an organ are stained using H&E staining technique. One slide per staining batch is selected and effects of staining variations are captured for a

complete cycle of staining. The stained tissue slides are scanned using a high resolution scanner to obtain digital slide images of the stained tissue slides. Each digital slide image is analyzed to extracted parameters of the digital slide images. Thereafter, the digital slide images are ranked or arranged in a descending order of accuracy. Based on the ranking, a digital slide image with the highest accuracy or rank is selected as a master slide image for the organ.

[0041] Moving on, image analysis engine 102 compares each parameter of a set of parameters of the digital slide image with a threshold value associated with the master image. The set of parameter can include two or more of, but is not limited to, tissue region red max pixel value, tissue region green max pixel value, tissue region blue max pixel value, brightness (gray image pixel value), non-tissue region value, tissue region red contrast, tissue region green contrast, tissue region blue contrast, sharpness measure (identify blurring), gamma value, out of focus percentage (%) and artifacts percentage (%). The threshold value is one or more of a first threshold value and a second threshold value, wherein the first threshold value is greater than the second threshold value.

[0042] For determining if the digital slide image is of acceptable quality or not, the threshold value needs to be defined manually or automatically. A user of system 100 may define a threshold value for each parameter of the set of parameters. Additionally, image analysis engine 102 is also configured to automatically define a threshold value for each parameter of the set of parameters. Image analysis engine 102 is configured to extract parameters of the plurality of digital slide images and the master slide image and to arrange the plurality of digital slide images in an increasing order of a parameter value such as, but not limited to, a peak color value.

[0043] Image analysis engine 102 is configured to categorize the plurality of digital slide images into three image classes based on the threshold values. The three image classes are a shoulder class (correction band), a zero correction class (zero correction band) and a toe class (correction band). Image analysis engine 102 is configured to perform analysis to categorize each parameter of the set of parameters into the three image classes and to store threshold values for each parameter. Image analysis engine 102 is configured to

compare parameter values of a digital slide image with the threshold value for each parameter for categorizing the digital slide image into a corresponding image class. Image analysis engine 102 is configured to categorize the digital slide images depending upon accuracy and parameter limits for each image class.

[0044] FIG. 2 shows a graphical representation of the image classes. Digital slide images from a band of parameters (as shown in FIG. 2) above a center region are considered to be in the shoulder class. Accuracy of the shoulder class is relatively significant compared to the master slide image at a starting point. However, the accuracy starts falling down drastically on moving upward towards the final end points of parameters. If parameter values of the digital slide image falls under the shoulder class, then the parameter values of the digital slide image is pushed to the parameters values of the master slide image. The upper control limit of the shoulder class is defined by a point beyond which if the parameter values exceed, system 100 may not be able to correct the digital slide images successfully.

[0045] Digital slide images from the band of parameters (as shown in FIG. 2) with accuracy close to the master slide image are considered to be in the zero correction class. Accordingly, the final end points of parameters are identified and set as limits for the zero correction class. The digital slide images in the zero correction class do not undergo any corrections in system 100. The automated digital image analysis is implemented directly for the zero correction band images.

[0046] Digital slide images from the band of parameters (as shown in FIG. 2) below the center region are considered to be in the toe class. Accuracy of the toe class is relatively significant compared the master slide image at the starting point. However, the accuracy starts falling down drastically on moving downward towards the final end points of parameters. If parameter values of the digital slide image falls under the toe class, then the parameter values of the digital slide image is pulled towards the parameters values of the master slide image. The lower control limit of the toe class is defined by a point beyond which if the parameter values exceed, system 100 may not be able to correct the digital slide images successfully.

[0047] Thus, if the digital slide image is categorized into the zero correction class, then the digital slide image does not require any further correction. The digital slide images in the zero correction class can be directly used by a personnel, physician or nurse for diagnosis. If the digital slide image includes parameter values between the shoulder class and the toe class, then the digital slide image is modified by image modifying engine 106. If the digital slide image includes parameter values above the shoulder class and below the toe class, then the digital slide image is analyzed by root cause analysis engine 108. The digital slide image which is provided to root cause analysis engine 108 are the discarded or rejected digital slide images.

[0048] If the digital slide image is of the acceptable quality, image modifying engine 106 is configured to modify the digital slide image. Image modifying engine 106 is configured to improve one or more characteristics of the digital slide image so as to fit the digital slide image for generating optimal algorithm output and enhance aesthetic appeal of the digital slide image for viewing purpose. Image modifying engine 106 is configured to modify one or more characteristics of the digital slide image based on the comparison of the digital slide image with the master slide image. Image modifying engine 106 is configured to modify one or more characteristics of the digital slide image based on the comparison of each parameter of the set of parameters of the digital slide image with the first threshold value and the second threshold value. The first threshold value corresponds to the shoulder class and the second threshold value corresponds to the toe class.

[0049] If the digital slide image is not of the acceptable quality, root cause analysis engine 108 is configured to identify a cause of error. Root cause analysis engine 108 is configured to associate one or more steps of generating the digital slide image and generating the stained tissue with the error. Root cause analysis engine 108 is configured to identify the cause of error based on root cause analysis information. The root cause analysis information includes an association between a plurality of causes and a plurality of errors. Further, the root cause analysis information includes an association between a plurality of errors and a plurality of steps associated with one or more of generating the

digital slide image and generating the stained tissue. The root cause analysis information is generated using information related to cause of variation in digital slide images. Generally, there is a possibility of variation from a predefined tissue preparation and staining procedure. Alternatively, the variation can be from acceptable environmental conditions during the staining procedure such as, but not limited to, temperature and humidity level. Due to the shift in standards, the quality of stained tissues being scanned to produce the digital slide images are degraded and affects image quantitative analysis. Table 1 describes various causes of the stain variation and possible corrections.

Table 1

Complaint	Cause	Correction
Hyperchromatic	Strong hematoxylin	Use lesser strength hematoxylin; Dilute
	(e.g., Harris full-	3:1 with ethylene glycol; Stain for less
	strength without	time; Differentiate in 0.25% Hydro
	acetic acid)	Chloride (HCl)
	Staining time too	Stain for less time
	long	
	Inadequate	Differentiate more;
	differentiation in	Use more concentrated HCl
	HCl	
	Differentiator	Replace more frequently
	exhausted	
Hypochromatic	Hematoxylin nearly	Replace hematoxylin
	exhausted	
	Staining too briefly	Increase staining time
	Over differentiation	Use weaker HCl
	in HCl Differentiate	
	less;	
	Progressive stain	Do not differentiate
	differentiated	·
	Paraffin sections	stain longer
	very thin Cut	
	thicker;	
	Regressive stain	Differentiate less
	over differentiated	
	Acid tap water, rare	Use distilled water
	(e.g., West Virginia)	
	Chlorine in tap water	Use distilled water
	(rare)	
	Bluing in acid tap	Use Scott's tap water substitute (TWS)
	water	

Wrong color:	Bluing too briefly	Blue longer
purple	Bluing solution exhausted	Change bluing solution daily
	No blue filter in microscope	Use microscope's "daylight" blue filter
Wrong color: gray	Colored impurities	Use BSC-certified hematoxylin
Wrong color: brown	Too much oxidizing agent	Use less [(e.g., 0.1 gram (gm)/gm hematoxylin]
	Over oxidized by long-term air exposure	Store with no air space and replace
Complaint	Cause	Correction
Wrong site: cytoplasm	Hematoxylin too concentrated; Under differentiation in HCl	Differentiate more; Stain less time or dilute
	RNA-rich cytoplasm	
Wrong site: nucleoli	Staining time too long	Stain less time
	Ineffective eosin Y	Use effective eosin Y
Hyperchromatic	Exceeds user expectations	Adjust expectations
	Insufficient subsequent alcohol rinses	Increase rinse time, dip more
	Stain-laden rinses	Use clean alcohol rinses
Wrong color: purple	Cytoplasm has retained hematoxylin applied regressively and partially differentiated	Use progressive hematoxylin or differentiate completely
	Insufficient subsequent alcohol rinses	Use three 95% ethanol (EtOH) baths, dip 10 times each
	Stain-laden rinses	Use clean alcohol rinses

[0050] The staining variations in Table 1 are represented in FIG. 3 that illustrates a fish bone diagram to represent the staining variations. The causes of staining variation are categorized into two main categories which are primary causes. The two main categories

of a cause are over staining and under staining. The primary cause is triggered by sub causes which are secondary causes such as, but not limited to, chemical concentration, staining time and other causes as indicated in Table 1. To find out the actual cause of variation, first a primary cause of variation is identified. Once the primary cause is identified, system 100 can narrow down the cause to the secondary cause and work on rectifying staining procedures.

[0051] Additionally, root cause analysis engine 108 is also configured to utilize a supervised learning approach of artificial neural networks for analyzing and identifying the change point in a staining environment. Alternatively, root cause analysis engine 108 is configured to use a supervised learning approach of artificial neural networks for bringing out faults in the staining procedure. The process of using the supervised learning approach of artificial neural networks involves data collection from conditions causing issues in image quantitative analysis implementation. The conditions can be one of, but not limited to, over staining, under staining, temperature variation and humidity variation. For each condition, there can be a deviation in parameters of a digital slide image from the master slide image. An input database (not shown in Fig. 1) store parameter deviations of images generated due to several conditions prevailing in the tissue preparation and the staining procedure. If a digital slide image is found to be classified into the toe class, the probable reasons for degradation of the slide quality is identified. Based on a repository knowledge and intelligence algorithm implementation, a corrective action is suggested in the digital slide image generation processes of a laboratory.

[0052] Further, root cause analysis engine 108 is configured to invoke for predicting probability of root cause for the digital slide image when the parameter values of the digital slide image is above the shoulder class or below the toe class.

[0053] FIG. 4 illustrates modules of root cause analysis engine 108. Root cause analysis engine 108 includes a feature extraction and selection unit 402 which is configured to extract parameters of digital slide images of over stained and under stained tissue along with normal images. The parameters are then provided as input to a classifier 404. Once classifier 404 is built at run time, classifier 404 can classify a digital slide image into one

of normal image, under image and over image. Images classified as normal image are passed on to algorithm for analysis. Images classified as under image or over image are rejected and a probable cause (error report) of an out-of-bound staining variation is predicted by a rule engine 406 based on rule engine configurations.

[0054] Root cause analysis engine 108 is configured to train classifier 404 using training data. The training data is generated using two modes. In a first mode, a user selects a master slide image for the laboratory and fixes a threshold (e.g. 10% or 20%) for allowed deviation in parameters with respect to the master slide image. The digital slide images falling within the threshold limit are qualified as normal images. The digital slide images which go beyond the threshold and above the master slide image values are considered over images. Similarly, the digital slide images falling beyond threshold and below master slide image values are considered as under images. FIG. 5 illustrates a graph representing staining variation classes with deviation of 20% from the master slide image. FIG. 5 shows a plot of images with blue mean values within 20% of the master slide image are declared as normal images, images above the threshold limit are over images, and images below the threshold limit are under images.

[0055] In a second mode, a new image is created from the master slide image by varying parameters of the master slide image and identifying values where a drastic change in parameters is observed. FIG. 6 shows a sample plot of master liver image red, green, blue channel histogram values varied from 0 to 255. A region in the sample plot where the peak intensity value of neither of a channel does not drastically fall to zero or suddenly shoots to maximum pixel value (i.e. 255) qualifies to be normal class intensity values. Images with mean pixel values falling below normal region pixel values qualify to be under images and images with mean pixel values falling above normal region pixel values qualify to be over images.

[0056] Further, root cause analysis engine 108 is configured to generate a report log when a digital slide image passes through system 100. The report log is stored in the form of either Extensible Markup language (XML) file or in database. If a digital slide image is classified as normal, then the original parameters along with modified parameters of

the digital slide image is stored. For images classified in over or under class by root cause analysis engine 108, an individual error report is created by rule engine 406. The error report can be stored in form of Portable Document Format (PDF) file or as an entry in the database. The error report includes information of parameters of the digital slide image and probable cause of degradation of stain. A laboratory manager can utilize the error report to improvise staining procedure in the laboratory. The error report is linked to the report log. Similarly, for images with discrepancy in organ detection by barcode and machine learning based algorithm output, a similar error report is generated specifying the discrepancy. Users can use filters to read separately the log of normal, over and under images. FIG. 7 shows a template of an error report generated for images classified as under image or over image.

[0057] FIG. 8 illustrates a flow diagram of a method for processing a digital slide image of a stained tissue in accordance with an embodiment of the invention. System 100 receives the digital slide image at step 802. Thereafter, system 100 determines an identifier associated with the digital slide image. An identifier associated with a digital slide image is used to determine a type of tissue associated with the digital slide image. As there is a possibility of error such as a clerical error in associating an identifier with a digital slide image, system 100 verifies the accuracy of the identifier associated with the digital slide image. A method of verifying an identifier associated with a digital slide image is explained in conjunction with FIG. 10.

[0058] In response to determining an identifier associated with the digital slide image, a master slide image is selected from a plurality of master slide images. Each master slide image in plurality of master slide images 104 is specific to a type of tissue. Therefore, a master image is selected based on an identifier (or a type of tissue) associated with a digital slide image.

[0059] Moving on, at step 804, the digital slide image is compared with the master slide image to determine if the digital slide image is of an acceptable quality. A digital slide image is of an acceptable quality when there is a scope to modify one or more characteristics of the digital slide image to obtain an enhanced digital slide image.

[0060] In order to determine the quality of the digital slide image, each parameter of a set of parameters of the digital slide image is compared with a threshold value associated with the master slide image. The set of parameter can include two or more of, but is not limited to, tissue region red max pixel value, tissue region green max pixel value, tissue region blue max pixel value, brightness (gray image pixel value), non-tissue region value, tissue region red contrast, tissue region green contrast, tissue region blue contrast, sharpness measure (identify blurring), gamma value, out of focus percentage (%) and artifacts percentage (%). The threshold value is one or more of a first threshold value and a second threshold value, wherein the first threshold value is greater than the second threshold value.

[0061] The digital slide image is categorized into one of three image classes based on the comparison of parameters of set of parameters of the digital slide image with corresponding threshold value for each parameter with respect to the three image classes. The three image classes are a shoulder class (correction band), a zero correction class (zero correction band) and a toe class (correction band). Each parameter of a digital slide image is compared with the threshold value for each parameter for categorizing the digital slide image into a corresponding image class. The digital slide image is categorized depending upon accuracy and parameter limits for each image class.

[0062] Thus, if the digital slide image is categorized into the zero correction class, then the digital slide image does not require any further correction. The digital slide images in the zero correction class can be directly used by a personnel, physician or nurse for diagnosis.

[0063] However, if the digital slide image includes parameter values between the shoulder class and the toe class, then the digital slide image is modified by image modifying engine 106 at step 806. One or more characteristics of the digital slide image are modified based on the comparison of the digital slide image with the master slide image.

[0064] In an embodiment, the digital slide image is modified by pushing or pulling one or more characteristics of the digital slide image to the shoulder class and the toe class (as described in system 100) to bring the digital slide image to a desired accuracy. A set of parameters of the master slide image are considered to be the zero reference level. One or more parameters of the set of parameters of the digital slide image are compared with the parameters of the master slide image. If a parameter of the digital slide image lies above the zero reference level, the parameter is pushed down to the zero level and if a parameter of the digital slide image lies below the zero reference level, the parameter is pulled upwards to the zero reference level.

[0065] In an embodiment, white balance of the digital slide image is modified. The quality of the digital slide image varies based on the image capturing device. Even if the same image-capturing device is used, variations are introduced in the image captured due to a control setting of the image capturing device. One of the reasons of variation is a light setting, used while capturing image, vary as per protocols of each laboratory. There are different optical microscopy illumination techniques such as, but not limited to, a bright field illumination. In the bright field illumination, regions out of a boundary of an organ region appear white with red, green, blue channel values at the maximum value under ideal condition. The maximum value is 255 for 8 bit per channel of an image. Generally, the images correctly acquired are visually very appealing and facilitates easy identification of structures within the slides. However, in practical scenario such result is not attained from digital slide images captured on run time due to deviation in image processing. Often times, the images acquired can have lesser brightness and density which makes the images lesser visually appealing. To compensate for the affect an image processing techniques, the white balance of the digital slide image is modified. The regions on the stain tissue slide which qualify as non-tissue regions are identified and the brightness value of the regions is pulled to an ideal value of maximum red, green and blue channel. In addition, a default gamma correction of 1.2 is performed to correct the density of every digital slide image.

[0066] On the other hand, if the digital slide image includes parameter values above the shoulder class and below the toe class, then the digital slide image is analyzed by root

cause analysis engine 108 to identify cause of error. The digital slide image which is provided to root cause analysis engine 108 are the discarded or rejected digital slide images.

[0067] The cause of error is identified based on root cause analysis information. The root cause analysis information includes an association between a plurality of causes and a plurality of errors. Further, the root cause analysis information includes an association between a plurality of errors and a plurality of steps associated with one or more of generating the digital slide image and generating the stained tissue. The root cause analysis information is generated using information related to cause of variation in digital slide images. This is further explained in conjunction with FIG. 9.

[0068] FIG. 9 illustrates a flow diagram of comparing a discarded or rejected digital slide image with the master slide image at run time in accordance with an embodiment of the invention. At step 902, a density plot of the discarded or rejected digital slide images is extracted. Thereafter, the density plot of the discarded digital slide image is compared with the density plot of the master slide image at step 904. Subsequently, the cause of error or deviation is identified at step 906. Finally, a correction in the steps associated with one of generating the digital slide image and generating the stained tissue is suggested at step 908.

[0069] For example, a correction is suggested in procedures of generating the digital slide image of lung tissue using H&E stain to adjust a procedure or step in a laboratory. The objective of procedure correction is to control staining variation within a defined band limit which is defined by the shoulder class and the toe class. The procedure correction can lead to acquire digital slide images which do not skips into range where system 100 may not be able correct the digital slide image properly. Hence, a new lab procedure can be suggested with only minor changes such as, change in the staining time period so as to bring down the variation in digital slide images to a defined range.

[0070] Fig. 10 illustrates a flow diagram of a method for verifying if an appropriate identifier is associated with a digital slide image. Modern histopathology slides generally

include an identifier such as a barcode pasted on the slide. The barcode includes information about the slide from which a user can decode organ information. Accordingly at step 1002, a type of tissue is determined based on an identifier associated with the digital slide image. In addition to barcode approach at step 1004,machine learning based automated organ detection module is used. Based on the characteristics of the digital image slide, an organ in the digital slide image is predicted. The characteristics can be texture or shape of tissue in the digital slide image. Thereafter, at step 1006, the tissue type (organ) determined based on the identifier and the organ predicted using the organ detection module is compared to determine a match. If both the results match, the identifier associated with the digital slide image is verified and further steps are performed. In case of mismatch between both the results, the digital slide image is discarded and a corresponding error report is generated. The digital slide image which are discarded due to mismatch can be analyzed manually later. If the digital slide image does not include barcode information, the organ identified by the machine learning based algorithm is relied upon.

[0071] Working example

[0072] The digital slide images generated in a histopathology laboratory are subjected to variation in staining due to number of factors such as, but not limited to, change in concentration of chemical, temperature change and organ affinity. FIG. 11 depicts examples of digital slide images which shows staining variation absorbed in a laboratory data. The variation in the digital slide images in FIG. 11 can be rectified by applying the invention. FIG. 12 depicts digital slide images corrected using the system in accordance with an embodiment of the invention. The invention deals with staining variation and other artifacts like tissue fold and dust particles introduced in process of digitalization of tissue slides. The invention creates master slide images, configures root cause analysis engine and corrects a digital slide image if required.

[0073] FIG. 13 illustrates a probable set of master slide images created by staining in ideal environment conditions and varying the staining time by (+/-) 10% and 20% from the standard staining time. The accuracy of each image is determined and the image with

maximum accuracy is selected as a temporary master slide image. FIG. 14 depicts the temporary master slide image. Image intensity values of the temporary master slide image are changed by 10 % and the effect is observed on an accuracy algorithm. The image with an intensity which gives higher accuracy compared to the temporary master slide image is stored as the new temporary master slide image. Image intensity values of the new temporary master slide image are changed with restricting of maximum 5% deviation and the effect is observed on the accuracy algorithm. The image with an intensity which gives maximum accuracy is stored as the final master slide image for an organ.

[0074] Once the master slide image is defined for each organ, root cause analysis engine is configured using a Root Cause Analysis (RCA) configuration tool. The RCA configuration tool is used to configure the root cause analysis engine which can be used to segregate images within standards and the images which fall outside a threshold value. The RCA configuration tool include an inbuilt functionality to generate a classifier which classifies digital slide images into three classes, namely, normal class, over class and under class. FIG. 15 illustrates functionality of a Root Cause Analysis (RCA) configuration tool. As illustrated in FIG. 15, the RCA configuration tool includes areas such as, training data folder, tolerance, RCA image configuration and user information. The training data folder provides a text box to specify the location where root cause analysis engine data needs to be stored. The tolerance provides a combo text box to specify the tolerance limit set for parameters to qualify a digital slide image as an acceptable quality image. The options provided in the combo box of the tolerance are "Auto", "5%" and "10%". If "Auto" option is selected, an intelligent algorithm determines the tolerance limit. If "5%" option is selected, a maximum deviation of 5% from the master slide image is allowed. If "10%" option is selected, a maximum deviation of 10% from the master slide image is allowed. The RCA images configuration provides combo box setting facilities to automatically generate images required to configure root cause analysis engine or to manually load images used in root cause analysis classes. The options provided in the combo box of the RCA images configuration are "Auto" and "Manual". If "Auto" option is selected, training data

required for root cause analysis engine is automatically generated as per the tolerance limit set by the user. If "manual" option is selected, the training data is overridden by replacing default images with user defined images in corresponding root cause analysis classes.

[0075] In addition, an option is provided to enable or disable the out of focus region ratio calculation. Further, a number can be provided by the user in a textbox which defines the sensitivity of the RCA to out of focus region areas. An out of focus ratio value implies the ratio of tissue region which is out of focus to the whole tissue region. If the out of focus region exceed the sensitivity value set by the user, a RCA report is generated. Further, an option is also provided to enable or disable the artifact region ratio calculation. A number can be provided by the user in a textbox which defines the sensitivity of RCA to artifact region areas. An artifact ratio value implies the ratio of tissue region including artifacts to the whole tissue region, wherein the artifacts can be, but is not limited to, tissue fold, dust particles, hairs and air bubbles. If the artifact region ratio exceed the sensitivity value set by user a RCA error report is generated. The user information provides a text box where a user can provide metadata information about staining. The RCA configuration tool also provides configure button and close button. When user selects the configure button, a machine learning based root cause analysis engine is built and the root cause analysis engine can be utilized for identifying out of bound images. The close button is used to close the RCA configuration tool.

[0076] After building the root cause analysis engine, digital slide images are provided as an input to the system of the invention. The name associated with each digital slide image is identified and parameters of each digital slide image are extracted. The parameters includes prominent red pixel value, prominent green pixel value, prominent blue pixel value, prominent gray image pixel value (image brightness), standard deviation of red channel pixels, standard deviation of green channel pixels, standard deviation of blue channel pixels, sharpness measure to identify blurring, out of focus percentage (%) and artifacts percentage (%). The root cause analysis engine compares parameters with respect to master slide image parameters and classifies the digital slide image into either normal, over or under based on analysis. The system identifies that images classified as

normal images are required to be adjusted: The characteristics which are required to be adjusted are prominent red pixel value, prominent green pixel value, prominent blue pixel value, prominent gray image pixel value (image brightness), out of focus percentage (%) and artifacts percentage (%). An error report is generated of the images classifies as over and under images. Based on calculated parameters and sets of rule specified, the system predicts possible cause of staining variation and generates a corresponding error report.

[0077] Another tool used in the system is an imagesmart configuration tool. The imagesmart configuration tool is a user interface tool built to facilitate configuration of imagesmart. FIG. 16 illustrates functionality of the imagesmart configuration tool. The imagesmart configuration tool includes areas such as, Image Smart folder, Folder verification button, Master Creation button and RCA Engine Configuration button. The Image Smart folder provides a text box to specify the location where the imagesmart configuration needs to be loaded. The Master Creation provides a configuration button to load another user interface which facilitates selection of master image. The RCA engine configuration provides a configuration button to load another user interface which facilitates configuration of root cause analysis engine.

[0078] The Imagesmart configuration tool also provides a user interface tool built to facilitate easy run of the system on set of images stored in an input folder. FIG. 17 illustrates functionality of ImageSmart tool. The ImageSmart configuration tool includes areas such as Lab Name, ImageSmart Configuration, Load Image Smart button, Organ, Batch Mode, Input Image Folder, Output Image Folder, Apply button, Convert button, Report button and Algorithm button. The Lab Name is a combo box listing the names of laboratory for which the imagesmart is configured. The ImageSmart Configuration provides a configuration button to load another user interface which facilitates configuration of imagesmart. Load button loads the lab specific imagesmart into memory. The Organ provides a combo box loads list of organs and a user can select an organ from the list. The combo box of organ provides options "Auto" and "Organ name". If the user selects the option of "Auto" in the combo box of the organ, the organ in the digital slide image is automatically identified using a machine learning algorithm. If the user selects the option of "Organ name", then the user can manually select the organ name. The Batch

Mode checkbox is used to run imagesmart on set of images in folder or single selected file. The image input folder provides a text box to specify the location of digital slide images which are provided as an input. Optionally, the user can change the location path through typing down or the system can open a dialog box which facilitates selection of path. The output image folder also provides a text box to specify the location of the output folder where the processed images needs to be stored. Similar to the image input folder, the user can change the location path through typing down or the system can open a dialog box which facilitates selection of path for the output image folder. If the user selects the apply button, the system processes the digital slide images in lower resolution and stores the output. If the user selects the convert button, the system processes the digital slide images in full resolution and stores the output. If the user selects the report button, a report card is generated for the processed images. If the user selects the algorithm button, the system facilitates running of user algorithms.

[0079] In the following examples, the liver tissue is stained using H&E staining technique. FIG. 18 depicts a liver master image. Table 2 provides the characteristics of the liver master image.

Table 2

Properties	Master Value	Offset
Tissue Region Red Max pixel Value	182	0
Tissue Region Green Max Pixel Value	56	0
Tissue Region Blue Max Pixel Value	123	0
Brightness	120	0
Non Tissue Region Value	255	0
Tissue Region Red Contrast	23.76	0
Tissue Region Green Contrast	16.60	0
Tissue Region Blue Contrast	15.90	0
Sharpness Measure	1	0
Gamma Value	1.2	0

[0080] Example 1: Image classified as a normal image

[0081] FIG. 19 depicts a test image of a digital slide image which is classified into a normal image class. Table 3 provides characteristics of the normal image.

Table 3

Properties	Master Value	Test Image Value	Offset
Tissue Region Red Max pixel Value	182	184	-2
Tissue Region Green Max Pixel Value	56	51	5
Tissue Region Blue Max Pixel Value	123	111	12
Brightness	120	115	5
Non Tissue Region Value	255	210	45
Tissue Region Red Contrast	23.76	24.94	0
Tissue Region Green Contrast	16.60	11.68	0
Tissue Region Blue Contrast	15.90	12.39	0
Sharpness Measure	1	0.8	0.2
Gamma Value	1.2	1	0.2

[0082] The imagesmart modifies the characteristics of the test image to provide a converted image. FIG. 20 depicts a converted test image. The characteristics of the converted image are provided in Table 4.

Table 4

Properties	Master Value	Smart Image Value	Offset
Tissue Region Red Max pixel Value	182	182	0
Tissue Region Green Max Pixel Value	56	56	0
Tissue Region Blue Max Pixel Value	123	123	0
Brightness	120	120	0
Non Tissue Region Value	255	255	0
Tissue Region Red Contrast	23.76	24.94	0
Tissue Region Green Contrast	16.60	11.68	0
Tissue Region Blue Contrast	15.90	12.39	0
Sharpness Measure	1	1	0
Gamma Value	1.2	1.2	0

[0083] Example 2: Image classified as an under image

[0084] FIG. 21 depicts a test image of a digital slide image which is classified into an under image class. Table 5 provides characteristics of the utider image.

Table 5

Properties	Master	Test	Offset
	Value	Image	

		Value	
Tissue Region Red Max pixel Value	182	148	34
Tissue Region Green Max Pixel Value	56	52	4
Tissue Region Blue Max Pixel Value	123	129	-6
Brightness	120	110	10
Non Tissue Region Value	255	211	44
Tissue Region Red Contrast	23.76	24.94	0
Tissue Region Green Contrast	16.60	11.68	0
Tissue Region Blue Contrast	15.90	12.39	0
Sharpness Measure	1	0.8	0.2
Gamma Value	1.2	1	0.2

[0085] As the tissue region red maximum pixel value of the under image is significantly more compared to the master image value, the under image is classified in under category image and correspondingly error report is generated. Based on rule engine algorithm, the system provides a suggestion that the image is categorized as under image due to higher concentration of Hematoxylin chemical during staining.

[0086] Example 3: Image classified as an over image

[0087] FIG. 22 depicts a test image of a digital slide image which is classified into an over image class. Table 6 provides characteristics of the over image.

Table 6

Properties	Master Value	Test Image Value	Offset
Tissue Region Red Max pixel Value	182	255	-73
Tissue Region Green Max Pixel Value	56	54	2
Tissue Region Blue Max Pixel Value	123	125	-2
Brightness	120	127	-7
Non Tissue Region Value	255	200	55
Tissue Region Red Contrast	23.76	24.94	0
Tissue Region Green Contrast	16.60	11.68	0
Tissue Region Blue Contrast	15.90	12.39	0
Sharpness Measure	1	0.8	0.2
Gamma Value	1.2	1	0.2

[0088] As the tissue region red maximum pixel value of the over image is significantly less compared to the master image value, the over image is classified as over image and correspondingly error report is generated. Based on rule engine algorithm, the system

provides a suggestion that the image is categorized as an over image due to low concentration of Eosin chemical during staining.

[0089] Example 4: Image classified as a high artifacts image

[0090] FIG. 23 depicts a test image which is classified as a high artifacts image. The test image which is classified as the high artifacts image includes regions marked in green color annotation indicating tissue folds and other artifacts. Consider that the user sets the artifact sensitivity as 5%. The ratio of artifacts and tissue regions is 9 % which is higher than the 5% artifact sensitivity set by the user. Thus, a corresponding error report is generated.

[0091] Example 5: Image classified as a high out of focus image

[0092] FIG. 24 depicts a test image which is classified as a high out of focus image. The test image which is classified as the high out of focus image includes regions marked in green color annotation indicating regions which are out of focus and unsuitable for analysis. Consider that the user sets the focus sensitivity as 5%. The ratio of out of focus regions is 27% which is much higher than the 5% out of focus sensitivity set by the user. Thus, a corresponding error report is generated.

[0093] In accordance with the method and system disclosed herein, a complete solution for handling issue of staining variation introduced due to imperfect laboratory process is provided. The method and system not only aides the correction of digital slide image to a specified standard, but also identifies drastic deviation in the laboratory process from a standard protocol. With the ability to predict the root cause and reasoning for degradation of quality with help of root cause analysis engine and image correction features, the method and system provides an important tool for any digital analysis system.

[0094] The system disclosed here can be configured to scale up for multiple laboratory settings. A user can provide a separate master image for each laboratory if the user needs to configure system separately for each individual laboratory. In addition, digital slide images can include a tag of a parent laboratory so as to invoke components corresponding

to the parent laboratory. Additionally, the system can configured to act as a global system for laboratories with coinciding properties.

[0095] Those skilled in the art will realize that the above recognized advantages and other advantages described herein are merely exemplary and are not meant to be a complete rendering of all of the advantages of the various embodiments of the invention.

[0096] In the foregoing specification, specific embodiments of the invention have been described. However, one of ordinary skill in the art appreciates that various modifications and changes can be made without departing from the scope of the invention as set forth in the claims below. Accordingly, the specification is to be regarded in an illustrative rather than a restrictive sense, and all such modifications are intended to be included within the scope of the invention. The benefits, advantages, solutions to problems, and any element(s) that may cause any benefit, advantage, or solution to occur or become more pronounced are not to be construed as a critical, required, or essential features or elements of any or all the claims. The invention is defined solely by the appended claims including any amendments made during the pendency of this application and all equivalents of those claims as issued.

CLAIMS

We claim:

1. A method for processing a digital slide image of a stained tissue, the method comprising:

receiving the digital slide image for processing;

comparing the digital slide image with a master slide image to determine if the digital slide image is of an acceptable quality, wherein determining if the digital slide image is of the acceptable quality comprises comparing each parameter of a set of parameters of the digital slide image with a threshold value;

modifying the digital slide image in response to determining that the digital slide image is of the acceptable quality, wherein modifying the digital slide image comprises modifying at least one characteristic of the digital slide image based on the comparison of the digital slide image with the master slide image; and

identifying a cause of error in response to determining that the digital slide image is not of the acceptable quality, wherein identifying the cause of error comprises utilizing a root cause analysis information.

- 2. The method of claim 1, wherein the stained tissue is obtained using at least one of a Hematoxylin and Eosin (H&E) stain, a Masson's Trichrome stain, a modified Grocott's Methenamine Silver (GMS) silver stain, a Periodic Acid Schiff (PAS), a Perls' Prussian Blue, a Ziehl Neelsen, an Alcian blue, a Gomori Trichrome (blue), a Mucicarmine, a Congo red, a Cresyl Violet Stain, a Luxol Fast Blue (MBS) Stain, an Alizarin Red S Stain, a Perls' Prussian Blue Stain, a Giemsa Stain, an Oil-Red-O, a Phloxine-B, Sudan Black, a Toluidine Blue Stain and a Von Kossa.
- 3. The method of claim 1, wherein the master slide image is selected from a plurality of master slide images, wherein each of the plurality of master slide images is associated with a type of tissue.

4. The method of claim 3, wherein the master slide image is selected based on an identifier associated with the digital slide image, wherein the identifier is used to determine a type of tissue associated with the digital slide image.

- 5. The method of claim 4, further comprising verifying the association between the type of tissue and the digital slide image, wherein the verification is performed by analyzing the digital slide image.
- 6. The method of claim 3, wherein associating a master slide image with a type of tissue comprises:

collecting a plurality of digital slide images for the type of tissue; ranking the plurality of digital slide images based on a predetermined criteria; and selecting a digital slide image of the plurality of the digital slide images as the master slide image for the type of tissue based on the ranking.

- 7. The method of claim 1, wherein the threshold value is defined by a user.
- 8. The method of claim 1, wherein the threshold value is at least one of a first threshold value and a second threshold value, wherein the first threshold value is greater than the second threshold value.
- 9. The method of claim 7, wherein the at least one characteristic of the digital slide image is modified in response to comparing each parameter of the set of parameters of the digital slide image with the first threshold value and the second threshold value.
- 10. The method of claim 1, wherein the root cause analysis information comprises an association between a plurality of causes and a plurality of errors.

11. The method of claim 1, wherein the root cause analysis information further comprises an association between a plurality of errors and a plurality of steps associated with at least one of generating the digital slide image and generating the stained tissue.

- 12. The method of claim 11, wherein identifying the cause of error comprises identifying at least one step of the plurality of steps associated with the error.
- 13. A system for processing a digital slide image of a stained tissue, the system comprising:

an image analysis engine configured to:

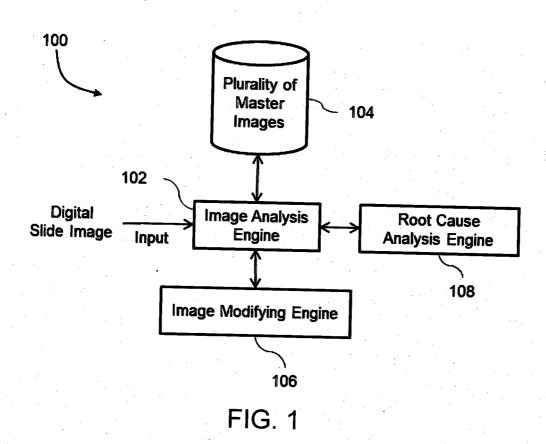
receive the digital slide image for processing; and

compare the digital slide image with a master slide image to determine if the digital slide image is of an acceptable quality, wherein determining if the digital slide image is of the acceptable quality comprises comparing each parameter of a set of parameters of the digital slide image with a threshold value;

an image modifying engine configured to modify the digital slide image in response to determining that the digital slide image is of the acceptable quality, wherein modifying the digital slide image comprises modifying at least one characteristic of the digital slide image based on the comparison of the digital slide image with the master slide image; and

a root cause analysis engine configured to identify a cause of error in response to determining that the digital slide image is not of the acceptable quality, wherein identifying the cause of error comprises utilizing root cause analysis information.

14. The system of claim 13, wherein the root cause analysis engine is configured to associate at least one step of at least one of generating the digital slide image and generating the stained tissue with the error.



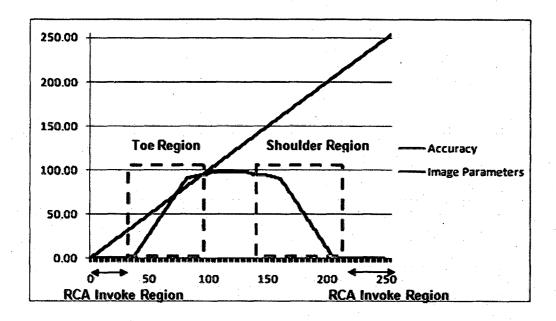


FIG. 2

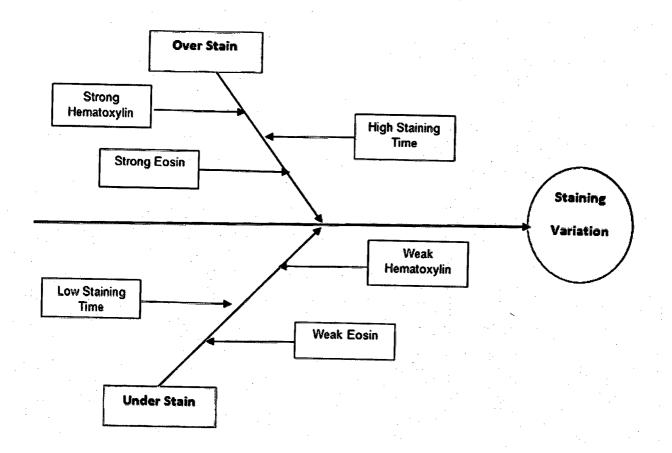


FIG. 3

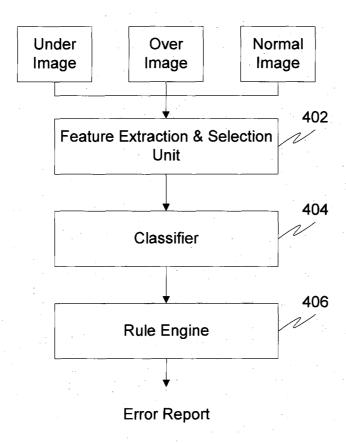


FIG. 4

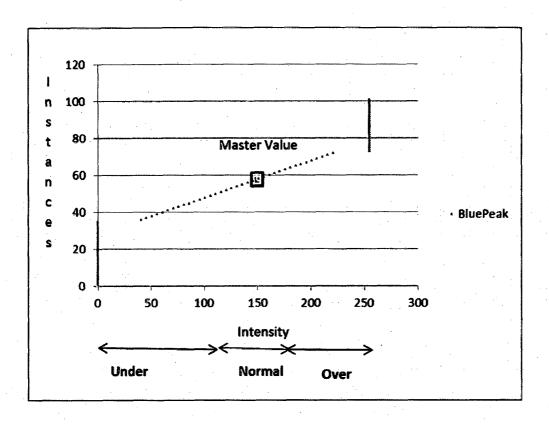


FIG. 5

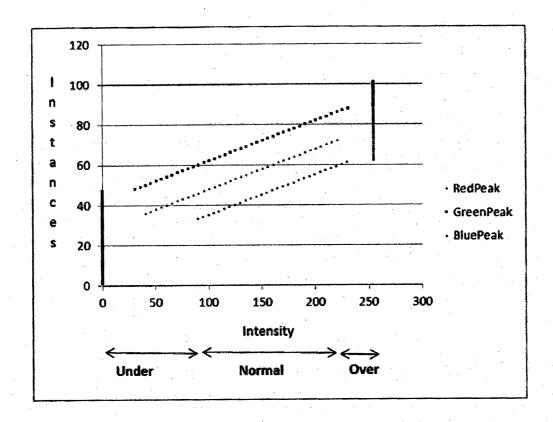


FIG. 6

RCA Reports		ImageCollection_0000000315_20 13-03-01 15_56_30.png
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FIG. 7

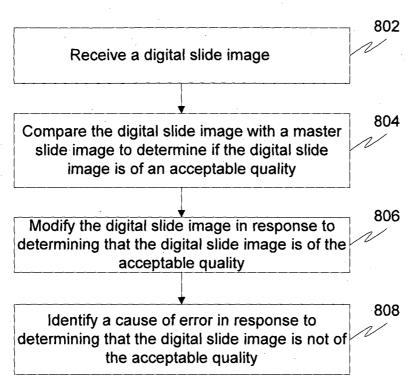


FIG. 8

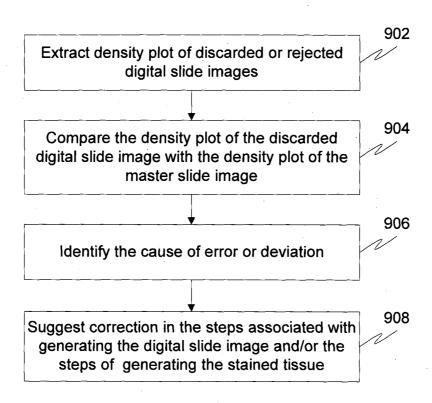


FIG. 9

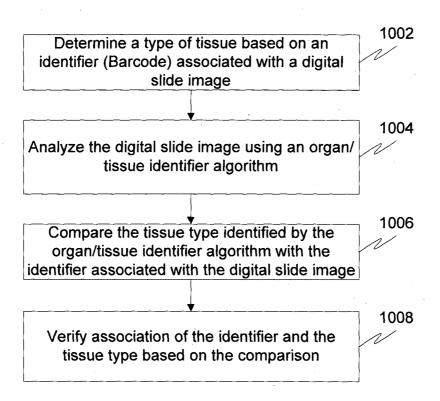


FIG. 10

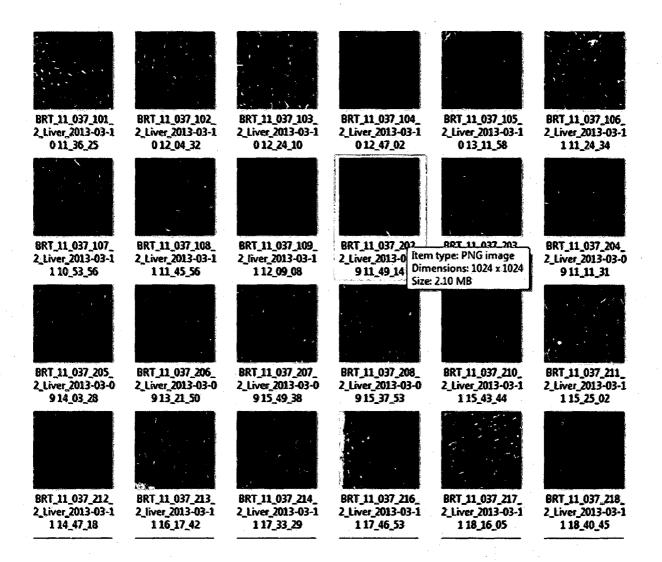


FIG. 11

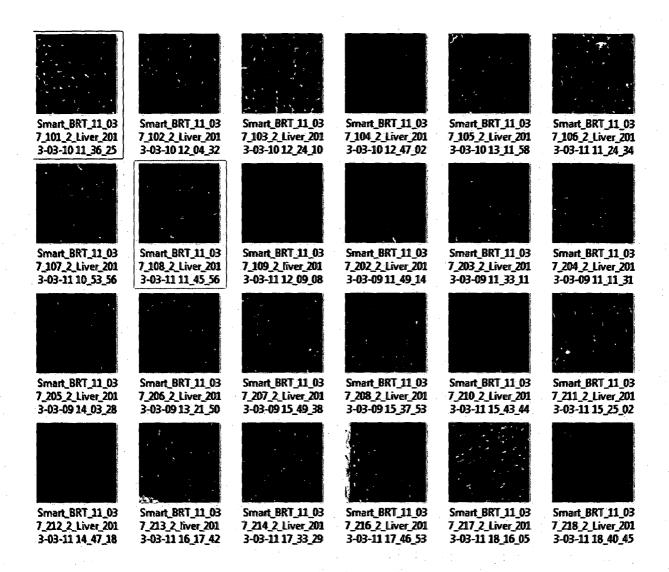


FIG. 12

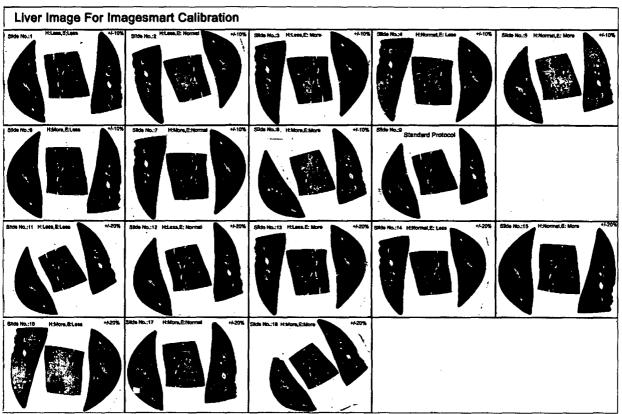


FIG. 13

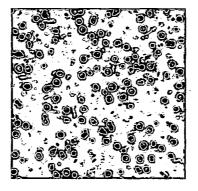


FIG. 14

Fraining Data Folder:	D:/ImageSmart/RCA	ngeSmart/RCA	
Stain Upper Tolerance:	10% ▼		
Stain Lower Tolerance:	10%		
RCA Images Configuration	Auto ▼		
Check Out of Focus			
Out of Focus Sensitivity	10 %	***************************************	
Check Artifacts			
Artifact Sensitvity	6 %	***************************************	
User Information:	Temp: 25°C Stainning Time: 2 min Staining Cycle: 1		
Configure		Close	

FIG. 15

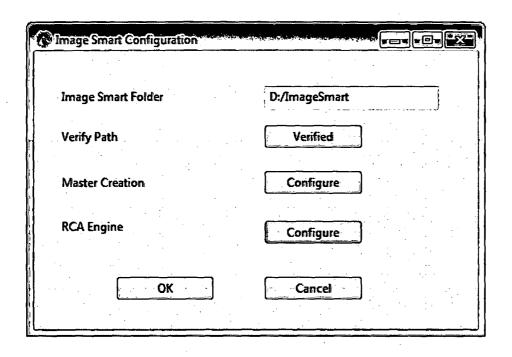


FIG. 16

Image Smart App Lab Help	
Lab Name	Sparc ▼
Image Smart Configuration	Configure
Load Image Smart	Load
Organ	Liver -
Batch Mode	
Input Folder	D:/Liver
Output Folder	D:/Smartimages
Apply Convert	Report Algorithm

FIG. 17

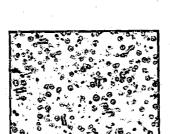


FIG. 18

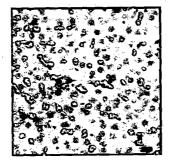


FIG. 19

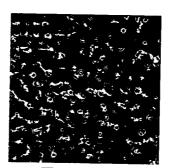


FIG. 20

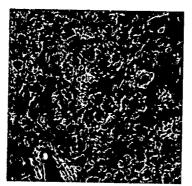


FIG. 21

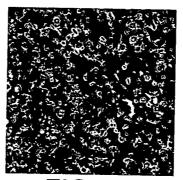


FIG. 22



FIG. 23

