

(51) International Patent Classification:
G06K 9/00 (2006.01)(21) International Application Number:
PCT/US2014/014298(22) International Filing Date:
31 January 2014 (31.01.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/759,201 31 January 2013 (31.01.2013) US
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999 Peachtree Street, Suite 1000, Atlanta, GA 30309 (US).(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM,
ZW.(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).**Published:**

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))
- with information concerning one or more priority claims
considered void (Rule 26bis.2(d))

(54) Title: METHODS AND SYSTEMS FOR VESSEL BIFURCATION DETECTION

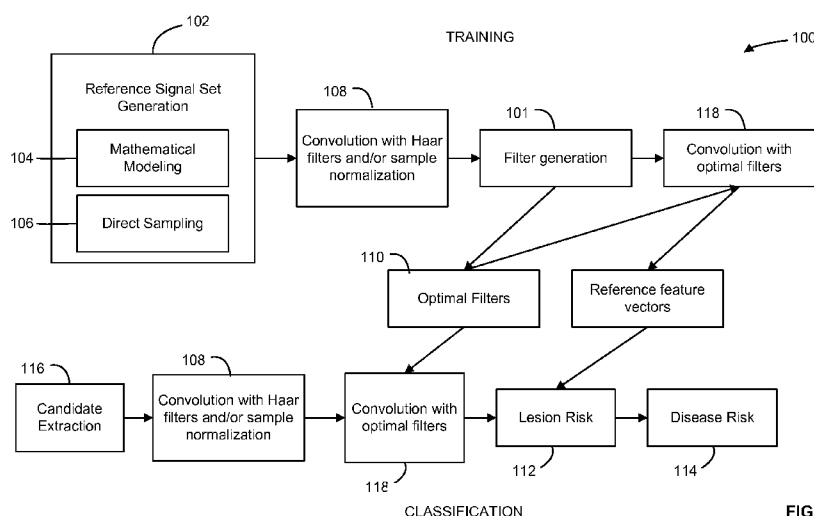


FIG. 1

(57) **Abstract:** Provided are systems and methods for analyzing images. An exemplary method can comprise receiving at least one image having one or more annotations indicating a feature. The method can comprise generating training images from the at least one image. Each training image can be based on a respective section of the at least one image. The training images can comprise positive images having the feature and negative images without the feature. The method can comprise generating a feature space based on the positive images and the negative images. The method can further comprise identifying the feature in one or more unclassified images based upon the feature space.

METHODS AND SYSTEMS FOR VESSEL BIFURCATION DETECTION

CROSS REFERENCE TO RELATED PATENT APPLICATIONS

- [0001] This application claims priority to U.S. Provisional Application No. 61/759,201, filed on January 31, 2013, and is a continuation-in-part of U.S. Non-provisional Application No. 13/992,552, filed on June 7, 2013, which is a national phase of PCT/US2011/063537, filed on December 6, 2011, which claims priority to U.S. Provisional Application No. 61/420,497 filed December 7, 2010, herein incorporated by reference in their entireties.

BACKGROUND

- [0002] Automated detection of objects of interest in images has rapidly expanded in the last decade. For example, lesions caused by disorders of the eye, especially Diabetic Retinopathy (DR) and Age-related Macular Degeneration (AMD) can be detected through image analysis. One important motivation is the need for reproducible, efficient, early detection, or screening, of large at-risk populations. In particular, there is a preponderance of evidence that early detection and timely treatment of DR, the most common cause of blindness in the working age population of the United States and of the European Union, can prevent visual loss and blindness in patients with diabetes.
- [0003] Most conventional efforts have focused on automatically detecting the lesions in color fundus photographs, as this is a non-invasive and cost-effective modality. One study of a large screening dataset has shown that, even though some automated detection algorithms achieve a detection performance comparable to that of human experts, further improvements are desirable before translation into clinical practice. A primary step in automated detection of DR is the detection of microaneurysms, which are highly pathognomic and often the first sign of DR, although it has been shown that detecting other lesions can improve DR detection performance. However, current methods fail to sufficiently differentiate lesions from retinal blood vessels: when a more sensitive setting was used, false positives occurred on the vessels, while when a specific setting was used, lesions connected to or close to the vasculature were missed.
- [0004] Several automated detection algorithms for detecting the lesions of AMD, the most common macular disease associated with aging and the most important

cause of blindness and visual loss in the developed world, have also been published. In particular, these efforts have focused on drusen, the hallmark of AMD. One of the main challenges in detecting drusen is the ability to differentiate them from bright lesions caused by other diseases, in particular, DR's exudates and cotton wool spots, as well as subtle, drusen-like lesions such as the flecks related to Stargardt's disease. AMD tends to occur in older patients than Stargardt's disease, but both the individual drusen and flecks, as well as their distribution, are very similar.

[0005] Negative lesion confounders are typically structures that are similar looking, but not the target lesion such as vessel portions in the microaneurysm case and exudates, cotton-wool spots and Stargardt flecks in the drusen case. Positive lesion confounders are typically a subset of target lesions that are easily missed because positive lesions have specific properties that are substantially different from the standard case, but should still be detected. In the case of microaneurysm detection, these are microaneurysms connected to the vasculature, for example. In other words, negative lesion confounders are the false positives of simple detectors and positive lesion confounders are the false negatives of simple detectors. Typically, lesions are hardly detected if the lesions are not specifically modeled. In both cases, lesions that are proximate to other lesions, including being fused with these other lesions, also are positive lesion confounders.

[0006] Additionally, retinal vessel bifurcations can be landmarks in retinal images. Bifurcation metrics can aid clinical evaluation and can serve as input for downstream image processing, such as retinal image registration and branching analysis. Accordingly, system and methods for detecting and/or differentiating objects of interest such as lesions, bifurcations, abnormalities, and/or other identifiable objects or collections of pixels, are desirable.

SUMMARY

[0007] It is to be understood that both the following general description and the following detailed description are exemplary and explanatory only and are not restrictive, as claimed. In one aspect, provided are methods and systems for optimal, user-friendly, object background separation, wherein the systems and methods can indicate/detect characteristics of an image such as legions evidencing a disease.

[0008] In an aspect, a method of identifying an object of interest in digital images can comprise obtaining first samples of an intensity distribution of one or more

objects of interest in one or more of the digital images based upon one or more wavelength bands; obtaining second samples of an intensity distribution of confounder objects in one or more of the digital images, at a predetermined frequency; transforming the first and second samples into an appropriate first space; performing dimension reduction on the transformed first and second samples, whereby the dimension reduction of the transformed first and second samples generates an object detector; transforming one or more of the digital images into the first space; performing dimension reduction on the transformed digital images, whereby the dimension reduction of the transformed digital images generates one or more reduced images; classifying one or more pixels of the one or more reduced images based on a comparison with the object detector; and identifying one or more objects of interest in the reduced digital images from the classified pixels.

[0009] In another aspect, a method of identifying an object of interest in a plurality of digital images configured as an image group can comprise: obtaining first samples of an intensity distribution of one or more objects of interest in the image group based upon one or more wavelength bands; obtaining second samples of the intensity distribution of confounder objects in the image group, at a frequency high enough to affect a pre-defined performance metric; transforming the first and second samples into an appropriate first space; performing dimension reduction on the transformed first and second samples, whereby the dimension reduction of the transformed first and second samples generates an object detector; transforming the image group into the first space; projecting the transformed image group into the reduced dimension space to generate a reduced image group; classifying each pixel in the reduced image group with an appropriate neighborhood based on a comparison with the object detector; and automatically identifying one or more objects of interest in the reduced image group from abnormal pixels based upon the comparison with the object detector.

[0010] In a further aspect, a system can comprise a memory for storing digital images; and a processor in communication with the memory, the processor configured to: obtain first samples of an intensity distribution of one or more objects of interest in one or more of the digital images based upon one or more wavelength bands; obtain second samples of an intensity distribution of confounder objects in one or more of the digital images, at a predetermined frequency; transform the first

and second samples into an appropriate first space; perform dimension reduction on the transformed first and second samples, whereby the dimension reduction of the transformed first and second samples generates an object detector; transform one or more of the digital images into the first space; perform dimension reduction on the transformed digital images, whereby the dimension reduction of the transformed digital images generates one or more reduced images; classify one or more pixels of the one or more reduced images based on a comparison with the object detector; and identify one or more objects of interest in the reduced digital images from the classified pixels.

[0011] In another aspect, exemplary methods can comprise receiving at least one image having one or more annotations indicating a feature. Methods can comprise generating training images from the at least one image. Each training image can be based on a respective section of the at least one image. The training images can comprise positive images having the feature and negative images without the feature. Methods can comprise generating a feature space based on the positive images and the negative images. Methods can further comprise identifying the feature in one or more unclassified images based upon the feature space.

[0001] In an aspect provided are methods of analyzing an image, comprising receiving an image, transferring the image into a feature space, and classifying one or more objects of interest in the transferred image as a bifurcation.

[0002] Additional advantages will be set forth in part in the description which follows or may be learned by practice. The advantages will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0003] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate embodiments and together with the description, serve to explain the principles of the methods and systems:

Figure 1 is a flow diagram of an exemplary method;

Figure 2 is an exemplary representation of image samples;

Figure 3 is a flow diagram of an exemplary method;
Figure 4 is a flow diagram of an exemplary method;
Figure 5 is a flow diagram of an exemplary method;
Figure 6 is a block diagram of an exemplary computing system;
Figures 7A-7D are exemplary image samples;
Figure 8 is a representation of an exemplary image determination;
Figure 9 is a graph of FROC of microaneurysm detection;
Figures 10A-10D are exemplary graphs of time complexity assessments;
Figure 11 is an exemplary graph of ROC of microaneurysm detection;
Figure 12 is an exemplary graph of ROC of drusen versus flecks classification;
Figure 13A illustrates an overview of an exemplary filter framework comprising two stages;
Figure 13B illustrates an example fundus image with annotated bifurcations labeled by dark circles;
Figure 13C illustrates bifurcation samples, and in red, green, and blue channels;
Figure 14 illustrates example filters based on the example data;
Figure 15 is an example plot of the cumulative variance of red, green, and blue channels with respect to the number of principal components;
Figure 16A illustrates an AUC curve of test images with 10 selected features;
Figure 16B illustrates an example probability map of example data;
Figure 16C illustrates vein bifurcations detected by the methods described herein;
Figure 17 is a flowchart illustrating an exemplary method of analyzing an image;
and
Figure 18 is a flowchart illustrating an exemplary method of analyzing an image.

DETAILED DESCRIPTION

[0004] Before the present methods and systems are disclosed and described, it is to be understood that the methods and systems are not limited to specific synthetic methods, specific components, or to particular compositions. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[0005] As used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise.

Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

- [0006] “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.
- [0007] ‘Optimal’ means that objects in background are detected equal than or better than any other method using the same user input.
- [0008] An “object” can be, for example, a regular or irregular region in an image with defined borders contained within a digital image. An “object of interest” can be, for example, an object that most closely resembles the concept that the user(s) are interested in detecting, for example, in a background. In the case of medical diagnosis, objects of interest can be lesions or abnormalities. In the case of retinal diagnosis, objects of interest can be, but not limited to, microaneurysms, dot hemorrhages, flame-shaped hemorrhages, sub-intimal hemorrhages, sub-retinal hemorrhages, pre-retinal hemorrhages, micro-infarctions, cotton-wool spots, yellow exudates, and the like.
- [0009] A “feature” can be, for example, a group of one or more descriptive characteristics of objects of interest. A “set of features” can be, for example, a customized group of one or more descriptive characteristics of objects of interest.
- [0010] A “threshold” can be, for example, a level, point, or value above which something is true or will take place and below which it is not or will not, such levels, points, or values include probabilities, sizes in pixels, and values representing pixel brightness, or similarity between features. “Background” can be, for example, some or all the regions in all images that are not objects of interest.
- [0011] A “supervised procedure” can be, for example, a computer programming method wherein a program learns a function from examples of inputs and outputs.
- [0012] Throughout the description and claims of this specification, the word

“comprise” and variations of the word, such as “comprising” and “comprises,” means “including but not limited to,” and is not intended to exclude, for example, other additives, components, integers or steps. “Exemplary” means “an example of” and is not intended to convey an indication of a preferred or ideal embodiment. “Such as” is not used in a restrictive sense, but for explanatory purposes.

[0013] Disclosed are components that can be used to perform the disclosed methods and systems. These and other components are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these components are disclosed that while specific reference of each various individual and collective combinations and permutation of these may not be explicitly disclosed, each is specifically contemplated and described herein, for all methods and systems. This applies to all aspects of this application including, but not limited to, steps in disclosed methods. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the disclosed methods.

[0014] The present methods and systems may be understood more readily by reference to the following detailed description of preferred embodiments and the Examples included therein and to the Figures and their previous and following description.

[0015] As will be appreciated by one skilled in the art, the methods and systems may take the form of an entirely hardware embodiment, an entirely software embodiment, or an embodiment combining software and hardware aspects. Furthermore, the methods and systems may take the form of a computer program product on a computer-readable storage medium having computer-readable program instructions (e.g., computer software) embodied in the storage medium. More particularly, the present methods and systems may take the form of web-implemented computer software. Any suitable computer-readable storage medium may be utilized including hard disks, CD-ROMs, optical storage devices, or magnetic storage devices.

[0016] Embodiments of the methods and systems are described below with reference to block diagrams and flowchart illustrations of methods, systems, apparatuses and computer program products. It will be understood that each block of the block diagrams and flowchart illustrations, and combinations of blocks in the

block diagrams and flowchart illustrations, respectively, can be implemented by computer program instructions. These computer program instructions may be loaded onto a general purpose computer, special purpose computer, or other programmable data processing apparatus to produce a machine, such that the instructions which execute on the computer or other programmable data processing apparatus create a means for implementing the functions specified in the flowchart block or blocks.

[0017] These computer program instructions may also be stored in a computer-readable memory that can direct a computer or other programmable data processing apparatus to function in a particular manner, such that the instructions stored in the computer-readable memory produce an article of manufacture including computer-readable instructions for implementing the function specified in the flowchart block or blocks. The computer program instructions may also be loaded onto a computer or other programmable data processing apparatus to cause a series of operational steps to be performed on the computer or other programmable apparatus to produce a computer-implemented process such that the instructions that execute on the computer or other programmable apparatus provide steps for implementing the functions specified in the flowchart block or blocks.

[0018] Accordingly, blocks of the block diagrams and flowchart illustrations support combinations of means for performing the specified functions, combinations of steps for performing the specified functions and program instruction means for performing the specified functions. It will also be understood that each block of the block diagrams and flowchart illustrations, and combinations of blocks in the block diagrams and flowchart illustrations, can be implemented by special purpose hardware-based computer systems that perform the specified functions or steps, or combinations of special purpose hardware and computer instructions.

[0019] In an aspect, the methods and systems disclosed can provide a way to detect objects in images, where the detectors for these objects are optimized. The methods can be used in a variety of applications, such as to detect abnormalities and other structures in retinal images, in other medical images, and in any other images, including robotic and computer vision as well as in online search. For example, results can be achieved in images of the retina, of blood cells, of fruit trees, and in satellite images of helicopter landing pads.

[0020] For example, if a user needs to find apples in images taken from the Internet,

the user can indicate a few example apples in a few images, the methods provided can then find the optimal detectors for apples, and can be used to quickly find apples in millions of images. Another advantage therefore is that no expert knowledge of the algorithm or image processing is needed, and the user only needs to be able to indicate the objects that are to be found.

[0021] With respect to retinal imaging, one problem with prior approaches is that normal tissue which resembles abnormalities were detected as abnormalities, while other abnormalities lying close to specific structures such as vessels are missed. In other words, the detectors are not optimal. The methods and systems described herein are substantially faster, and mimics quite closely the processing of visual information by the brain.

[0022] In an aspect, an optimal filter framework is provided to solve lesion segmentation and differentiation problems in retinal images, including but not limited to microaneurysm detection and drusen versus flecks differentiation. As an example, the optimal filter framework can provide detection that is as close to instantaneous as possible. As a further example, the optimal filter framework can allow instantaneous feedback to the camera operator, as well as immediate feedback of the detection results to the patient.

[0023] In an aspect, the optimal filter framework can automatically generate features adapted for differentiating target lesions, including atypical target lesions, from negative lesion confounders. As an example, the optimal filter framework can rely on the generation of a set of filters matched both to the lesions and to common positive as well as negative lesion confounders.

[0024] In an aspect, modeling lesions mathematically is convenient in the sense that no training images are required: the human brain is able to generalize out verbal descriptions by clinicians, though a limited number of samples can serve the modeler well. Moreover, no additional annotations are required each time the method is applied to a new dataset. On the other hand, deciding how to model the target lesions can be subjective and biased, and a good description may not (yet) be available. Therefore, fully automating the design is attractive, as it makes the disclosed approach immediately applicable to a wider range of lesion detection problems, and any modeling bias is avoided.

[0025] **FIG. 1** is a block diagram illustrating an exemplary method. This exemplary

method is only an example of an operative method and is not intended to suggest any limitation as to the scope of use or functionality of operating environment architecture. Neither should the operating environment be interpreted as having any dependency or requirement relating to any one or combination of components illustrated in the exemplary operating environment.

[0026] In an aspect, the method **100**, illustrated in **FIG. 1**, can comprise generating an optimal set of filters, at **101**, to differentiate objects of interest such as lesions and positive and negative lesion confounders, for example. As an example, an optimal filter framework for detecting target lesions can comprise obtaining a representative set of samples from one or more of lesions, positive lesion confounders, and negative lesion confounders, at **102**. As an example, a set of filters, or a basis, can be derived from the samples to optimally represent the samples. Although the description of **FIG. 1** is directed to lesions and lesion confounders, other objects of interests can be detected and differentiated in a similar manner using the systems and methods described herein.

[0027] In an aspect, the representative set of samples can uniformly describe the space of all possible samples (e.g., lesion samples), as well as the space of possible confounders (e.g., negative lesion). As an example, the most common lesion confounders can be sampled.

[0028] In an aspect, the design of an exemplary filter can be defined as one of the following:

1) expert-driven: a mathematical model can be designed by a modeler for both lesions and lesion confounders, and the model parameter space can subsequently be traversed to generate (different) artificial image samples; and

2) data-driven: a set of annotated image samples can be used.

[0029] In an aspect, the method of **FIG. 1** can comprise a training stage and a classification or test stage as shown, as shown in **FIG. 1**. As an example, during the training stage, a set of images (e.g., digital images with expert-annotated objects), can be used to build one or more object filters, and to optimize the classification.

[0030] In an aspect, internally the training set of images can be divided into a first subset and a second subset. As an example, the first subset can be used to build an optimal set of object filters. As a further example, the second subset can be used to

perform feature selection on the optimal set of object filter, resulting in selected filters. A classifier can be trained based on the selected filters, resulting in a trained vision machine for which the performance can be determined.

- [0031] In an aspect, during a test stage, the objects in a test images set (e.g., retinal images) can be detected and localized by the system and can be compared to the annotation of an expert. As an example, to maintain generality and robustness, one or more of the first and second subsets and the filters can be representative samples from the real data that can be kept entirely separated.
- [0032] In an aspect, by the framework(s) described herein, a set of filters can be obtained to form a feature space and reference points in the feature space. As an example, an unknown fundus image under detection can be first transferred into the feature space and each pixel can be assigned the probability of being a bifurcation, thus a soft probability map of bifurcations can be generated.
- [0033] The following description details the exemplary steps of various aspects of the disclosed framework(s), including the sample generation, filter generation, bifurcation detection, and feature selection.
- [0034] As explained above, both/either an expert driven (e.g., mathematical modeling **104**) and/or data-driven design (e.g., direct sampling **106**) approach can be used in order to obtain samples representative of the objects (e.g., lesion) of interest, as well as samples from positive lesions confounders, negative lesions confounders, or any combination of these.
- [0035] As an example, in the expert-driven approach (e.g., mathematical modeling **104**), a modeler can be configured to translate verbal descriptions with clinicians, as well as intensity distributions in a limited number of samples selected by the clinicians, into mathematical equations. In an aspect, the mathematical equations can be based upon a continuous model of the intensity distribution of the modeled lesions, and were defined for typical lesions, for positive lesion confounders if any are identified, and for negative lesion confounders, if any are identified. As a further example, the intensity profile of the lesions can be modeled by generalized Gaussian functions of normalized intensity, for example, such as the following function:

$$profile(r; \beta, \delta) = \delta e^{-r^\beta}$$

where r is the distance to the center of the profile divided by its standard deviation, β characterizes the sharpness of the contours and δ is the amplitude ($\delta = 1$ for drusen, $\delta = -1$ for microaneurysms).

[0036] In an aspect, the typical intensity distribution for both microaneurysms and drusen can be modeled as:

$$\begin{aligned} \text{typical}(x, y; \alpha_1, \alpha_2, \beta, \theta) &= \text{profile}(r; \beta, \delta) \\ u &= x \cos(\theta) + y \sin(\theta) \\ v &= -x \sin(\theta) + y \cos(\theta) \\ r &= \sqrt{\left(\frac{u}{\alpha_1}\right)^2 + \left(\frac{v}{\alpha_2}\right)^2} \end{aligned}$$

[0037] As an illustrative example, a plurality of image samples and samples derived from the models are provided in **FIG. 2**. Other images in various domains can be processed in a similar manner. Examples of image samples (first row **202**) and similar samples derived from mathematical models in the spatial domain (second row **204**) and after convolution with Haar filters (third row **206**: vertical Haar filter, fourth row **208**: horizontal Haar filter). The first six samples can come from the microaneurysm detection problem: a typical lesion (**a**), positive lesion confounders (**b**), (**c**) and negative lesion confounders (**d**), (**e**), (**f**). The last two samples come from the drusen (**g**) versus flecks (**h**) classification problem.

[0038] In an aspect, a negative microaneurysm confounder can be defined by a linear vessel portion. As an example, the negative microaneurysm confounder can be model by:

$$\text{linearVessel}(x, y; \alpha, \beta, \theta) = \text{profile}\left(\left|\frac{v}{\alpha}\right|; \beta, -1\right).$$

[0039] In an aspect, a negative microaneurysm confounder can be defined by a vessel branch: three linear segments, modeled by

$$\text{linearVessel}(x, y; \alpha, \beta, \theta) = \text{profile}\left(\left|\frac{v}{\alpha}\right|; \beta, -1\right),$$

can meet at the center of the model I , where the three intensity distributions, I_1 , I_2 and I_3 , are fused and can be empirically expressed as $I = (I_1 + 1)(I_2 + 1)(I_3 + 1) - 1$.

[0040] In an aspect, a negative microaneurysm confounder can be defined by a

vessel crossing: two vessels, modeled by

$$\text{linearVessel}(x, y; \alpha, \beta, \theta) = \text{profile}\left(\left|\frac{v}{\alpha}\right|; \beta, -1\right),$$

meet at the center of the model, where the two intensity distributions, I_1 and I_2 , are fused. Since the two vessels overlap, the intensity is darker at the center of the model I . As an example, the confounder can be empirically expressed as:

$$I = -\sqrt{I_1^2 + I_2^2}$$

[0041] In an aspect, positive lesion confounders for microaneurysm detection can be modeled by a translation of one or more of the following functions:

$$\text{typical}(x, y; \alpha_1, \alpha_2, \beta, \theta) = \text{profile}(r; \beta, \delta)$$

$$\text{linearVessel}(x, y; \alpha, \beta, \theta) = \text{profile}\left(\left|\frac{v}{\alpha}\right|; \beta, -1\right)$$

[0042] In an aspect, negative lesion confounders can be modeled for drusen detection. As an example, a pisciform intensity distribution can be used. As a further example, the pisciform intensity distribution can be used to model Stargardt's disease flecks, as illustrated below:

$$\text{fleck}_{|u>0}(x, y; \alpha_1, \alpha_2, \beta, \theta) = \text{profile}(r1; \beta, \delta)$$

$$\text{fleck}_{|u\leq 0}(x, y; \alpha_1, \alpha_2, \beta, \theta) = \text{profile}(r2; \beta, \delta)$$

$$r1 = \sqrt{\left(\frac{u}{\alpha_1}\right)^2 + \left(\frac{v}{\alpha_2}\right)^2}$$

$$r2 = \sqrt{\frac{u^2 + v^2}{\alpha_1^2}},$$

where $\text{fleck}_{|u>0}$ (resp. $\text{fleck}_{|u\leq 0}$) is the tail (resp. head) of the goldfish. As a further example, positive lesion confounders can be modeled for drusen detection.

[0043] In an aspect, once the intensity distribution of the lesions and lesion

confounders are modeled, samples can be generated from each intensity distribution model according to the exemplary method illustrated in **FIG. 3**. Although lesion detection is used as an example, other objects of interest can be used in various domains.

[0044] In step **302**, a scale for the generated samples can be selected based on an estimation of the typical size of the lesions and lesions confounders in images. As an example, the generated image samples can be defined as circular image patches of radius R times as wide as the typical lesion size (e.g., $R = 3$). As an example, a wide ratio R can be selected since most negative lesion confounders look similar to the lesions at the center of the patch. As a further example, lesions can be discriminated from negative lesion confounders by the periphery of the patch. As a further example, for microaneurysm detection, vessel crossings may look similar to a microaneurysm at the center, but, as opposed to microaneurysms, there will be linear structures, oriented toward the center of the patch, at the periphery.

[0045] In step **304**, for each parameter π_i of a model (the standard deviations α_1 and α_2 of the lesions, the angle between vessel segments, the distance between two neighboring lesions, etc.), a range $[\pi_i \text{ min}; \pi_i \text{ max}]$ of variation can be estimated from the training set.

[0046] In step **306**, image patches can be generated from each model by uniformly sampling the product space

$$\prod_i [\pi_i^{\text{min}}, \pi_i^{\text{max}}].$$

Although many parameters might be normally distributed across actual lesions, a uniform sampling ensures that rare lesions are equally well characterized. However, other samplings can be used.

[0047] In an aspect, a color model can be used to improve further the presented grayscale modeling of the lesions. As an example, gray levels in the generated samples are mapped to colors, using a look-up table (e.g. intensity 0 — the background—can be mapped to pale orange and intensity -1 — the center of vessels and microaneurysms—can be mapped to dark red, for example). If the scale range for the target lesion is very important, then different sizes of patches can be generated.

[0048] In an aspect, an advanced physical model of the lesion transform, e.g. the effect the local pathology has on overlying and surrounding tissue, can be created,

thus completely predicting the visual appearance of the lesions and lesion confounders. However, such a model would be highly complex, and more importantly, the model's design would require substantial domain knowledge, as well as a substantial amount of experiments to perfect the model for each new application. Modeling is even more challenging if color is involved: a direct sampling color model simply requires sampling in the entire color space, instead of complex modeling of the interaction of color channel intensities. Hence, a data-driven or direct sampling approach has many advantages.

[0049] In direct sampling, the target lesions (e.g., typical lesions and positive lesion confounders) can be annotated on a training dataset. As an example, the annotation can comprise an indication of the center of the lesions, or segment the lesions. In an aspect, a candidate lesion detector can be used to find a center of the lesion within the segmented region. As an example, a set of sample images can represent all images and all local image variations that the disclosed filter framework may encounter to optimize the framework.

[0050] Returning to **FIG. 1**, in an aspect, in order to increase the representativeness of the reference samples, one or more initial steps can be performed, at **108**. First, the variability due to the noise potentially embedded in the reference samples can be minimized. Second, the generality of the reference samples can be increased by a normalization process.

[0051] In an aspect, the presence of low-frequency noise (e.g., slow background intensity variation) and high-frequency noise (e.g., salt-and-pepper noise, compression artifacts, etc...) is typically a major problem for characterizing the appearance of lesions in retinal images. Accordingly, the noise-free samples S and/or noisy samples $S + N$ can be projected into a transformed space where the signal-to-noise ratio is high, such as

$$T(S) \approx T(S + N) \approx T(S + N'),$$

where T is the transform operator, and N and N' are two realizations of a random noise. As an example, image samples can be convolved with horizontal and vertical Haar filters, at **108**, dilated by a factor s to match the typical scale of the lesions (e.g., $s=2$).

[0052] In an aspect, representative samples characterize the range of variations for the shape, the intensity and the color of the target lesions and lesion confounders.

One of these parameters, the intensity of the object can easily be normalized across samples, at **108**. Normalizing this parameter reduces the dimensionality of the problem, without significantly affecting the quality of the image sample representation. In particular, a higher generalization ability can be achieved with the same number of image samples (see **FIG. 9**). As a consequence, fewer images need to be annotated. Normalizing the intensity of samples generated by a mathematical model can be trivial: the intensity at the center of the model simply can be set to one. Normalizing the intensity of samples directly extracted from images, on the other hand, is not: for a reliable estimation of the lesion intensity, the intensity distribution in the target sample is matched to the intensity distribution in the average sample using the least mean squared algorithm, in the transformed space of high signal-to-noise ratio. Finally, the intensity of each pixel in the transformed sample can be divided by its estimated intensity.

[0053] In an aspect, the reference samples for lesions and lesion confounders, can be projected in the transformed space of high signal-to-noise ratio and subsequently normalized. As an example, the reference samples can be maximally representative of all lesions and lesion confounders, provided that these are also projected into the transformed space and normalized. In the absence of time constraints, classifying a new sample can be reduced to finding the most similar reference samples, in a least square sense. In other words, the normalized transformed space described above can be used as feature space for classification with a k-NN classifier. Because it can be desirable to achieve close to instantaneous detection, the dimensionality of the feature space can be configured to be as low as possible. As an example, the reference samples can be relied upon to find the filters generating the optimal feature space for classifying new samples: a reduced feature space preserving information in the least square sense.

[0054] In an aspect, for any desired feature space dimension, the optimal projection for given samples (e.g., the transformed and normalized reference samples), in terms of information preservation in least square sense, can be provided by the Principal Component Analysis (PCA) of these samples. As an example, PCA is an orthogonal linear transformation that transforms the set of samples into a new coordinate system such that the greatest variance, by any projection of the data, comes to lie on the first coordinate, the second greatest variance on the second coordinate, etc.

- [0055] In an aspect, each sample can be considered as a single observation, through applying PCA on the set of samples, principal components can be obtained which can be the same size as the samples. These principal components can be the optimal filters because the linear combination of these filters represents the entire set of samples, and the coefficients of the linear combination can be obtained by the convolution of original samples with corresponding filters.
- [0056] The optimal filters thus found can span the initial, high dimensional feature space into which any image pixel can be projected. In an aspect, bifurcations in a training set can be projected into the feature space in this way to form the positive reference points. Non-bifurcation points can be randomly sampled in the training set and projected into the feature space in the same way to form the negative reference points. Both bifurcation and non-bifurcation points together can form the reference points in the feature space. For computational efficiency, sampled pixels from the training set can be projected into the initial feature space by convolving them with the filters for later usage.
- [0057] In an aspect, given a set of optimal filters **110**, previously unseen images and image regions can be classified within this optimal feature space. A so-called risk of presence of the target lesion can be derived for each of the image samples, at **112**. This risk can subsequently be used to segment the lesions in the image, or, to derive an automated probabilistic diagnosis for the entire image, at **114**.
- [0058] In an aspect, images can be processed based upon the method illustrated in **FIG. 4**. However, other sequences, steps, and processes, can be used and applied in various domains.
- [0059] In step **402**, a preprocessing step can be used to identify and normalize candidate target lesions in an image. In step **404**, for each pixel $p_{i,j}$ selected in the preprocessing step **402**, the normalized neighborhood of the pixel – the sample – can be input to the classifier. As an example, the risk of presence of the target lesion can be computed by the classifier for $p_{i,j}$ and a lesion risk map can thus be obtained, at **406**. In step **408**, if the lesions need to be segmented, the risk map defined in step **406** can be thresholded, and the connected foreground pixels can be identified using morphological labeling. Each connected component can be regarded as an automatically detected lesion, and this lesion can be assigned a risk value defined as the maximal pixelwise risk of presence within the connected component. In step

410, if a probabilistic diagnosis for the entire image is desired/required, the risks assigned to each automatically detected lesions can be fused. Typically, if a single type of lesions is detected, the probabilistic diagnosis for the image can simply be defined as the maximum risk of presence of a target lesion.

[0060] Returning to **FIG. 1**, in an aspect, a candidate extraction step **116** can be used for both selecting reference negative lesion confounders in the direct sampling and selecting the pixels that can be fed to the classifier when processing unseen images.

[0061] As more clearly shown in **FIG. 5**, the first step to extract candidates in an input image is to transform the image, at **502**. As an example, the techniques discussed at step **108** can be used to transform the image. However, other transforms can be used. For each pixel $p_{i,j}$ in the transformed image, the intensity of the potential lesion within the neighborhood $N_{i,j}$ of the pixel $p_{i,j}$ can then be estimated, at **504**. As an example, the techniques discussed at step **108** can be used to estimate intensity of pixels of the image. However, other estimation processes and methods can be used.

[0062] In step **506**, the intensity of the potential lesion can be compared to a threshold or pre-defined range value. If the intensity of the potential lesion is outside the normal range of intensities for the target lesions — the range observed on the training set plus a margin —, $p_{i,j}$ can be rejected as a potential lesion. As an example, candidates with low intensity can be discarded (the background): by chance, magnified background pixels might look similar to the target lesions; similarly, attenuated pigment clumps or attenuated small nevi might look like lesions, so candidates with an unusually high intensity can be discarded. If the lesion intensity is within that range, the neighborhood $N_{i,j}$ can be normalized (i.e. divided by the estimated intensity), at **508**, before being further classified.

[0063] As an example, when this candidate extraction step is used to select reference negative lesion confounders in the direct sampling approach, the candidate pixels $p_{i,j}$ can be selected using a manually tuned constant threshold on the average pixel-to-pixel squared distance to the average transformed and normalized positive lesion sample ($=0.3$).

[0064] Returning to **FIG. 1**, in an aspect, since the set of filters generating the optimal feature space, at **118**, can be derived from a representative set of lesions and

lesion confounders, a straightforward approach to classify new image samples within the optimal feature space can be to find the most similar representative samples within this space. A lesion risk can be computed (e.g., at **112**) for a new sample from the distance to these representative samples and their labels. As an example, the distance between two samples can simply be defined as the Euclidian distance between their projections on the optimal set of filters. Approximate nearest neighbor search, based on k-d trees, can be applied to find the most similar reference samples.

[0065] Once the k most similar samples $(r_i)_{i=1..k}$ of label $(l(r_i))_{i=1..k}$ have been found, the presence risk $\rho(s)$ is defined for the new sample s as follows:

$$\rho(s) = \frac{1}{k} \sum_{i=1}^k l(r_i) \exp(-||r_i - s||)$$

[0066] where

$l(r_i)=1$ if r_i is a target lesion (e.g., typical lesion or common positive lesion confounder) and $l(r_i)=-1$ if r_i is a common negative lesion confounder. This risk ranges from -1 (e.g., high risk of being negative) to 1 (e.g., high risk of being positive). If the new sample is neither a typical lesion nor a lesion confounder, then the distance to the most similar reference samples is likely to be high. As a consequence, a risk close to zero can be measured. In particular, if background pixels are not discarded by the candidate selection step, it is likely that a risk close to zero is measured.

[0067] In an aspect, if the set of reference samples is representative of the negative (resp. positive) lesion confounders, then false positives (resp. false negatives) should only occur for rare negative (resp. positive) lesion confounders. Accordingly, system performance and system complexity can be exchanged by adjusting the definition of “common” and “rare” lesion confounders.

[0068] In an aspect, after selecting the optimal filters and generating the reference points in the feature space, the optimal filters and reference points can be used to classify whether a pixel in a fundus image is a bifurcation. An image under detection

can be transferred into the feature space by being convolved with the optimal filters so each pixel corresponds to a query point. As an example, the k-Nearest Neighbor algorithm (k-NN) can be used to classify the query points. As a further example, Approximate Nearest Neighbor (ANN) can be applied to classify query points. In an aspect, soft classification and the probability of a query point to be a bifurcation can be calculated by $p = n/k$, in which k means the number of neighbors considered and n is the number of positive points among the k nearest neighbors. Thus, a probability map of the original image reflecting the probability of every pixel to be a bifurcation can be obtained. In an aspect, Even though the dimension of feature space can be the number of chosen optimal filters (i.e. PCs), the feature space is still a high dimensional space for classification. Accordingly, feature selection can be applied to select a few of most discriminative and efficient filters.

[0069] In an aspect, probability maps can be generated with different optimal filters chosen by Sequential Forward Selection (SFS) for each iteration. As an example, the metric can evaluate the probability maps and give the AUC for the ROC curve for the whole set of probability maps. As a further example, SFS first selects out one filter with the highest AUC, then adds a new filter from the remaining filters such that the two filters have the highest AUC. In an aspect, SFS can add a new filter from the remaining filters to give the highest AUC until the stop criteria of the feature selection is met. As an example, the feature selection stops when the number of selected filters reaches the maximal number of filters, or the AUC starts to decline.

[0070] In an aspect, a metric to give the AUC can be pixel-based. Since the probability map is soft labeled, the map can be thresholded to obtain a binary image and evaluate the binary image pixel by pixel. As an example, every pixel P is decided as true positive (TP), false positive (FP), true negative (TN) or false negative (FN) according to the pixel's distance to a bifurcation, which is shown by

$$P = \begin{cases} TP & \text{if } P \text{ is labeled and } |P - B| < D \\ FP & \text{if } P \text{ is labeled and } |P - B| > D \\ TN & \text{if } P \text{ is unlabeled and } |P - B| > D \\ FN & \text{if } P \text{ is unlabeled and } |P - B| < D \end{cases},$$

where $|P - B|$ is the distance between pixel P and any bifurcation B , and D defines

the region of bifurcations.

- [0071] As an example, when data is highly skewed that the number of negative points (non-bifurcation pixels) is much larger than that of positive points (i.e. bifurcation pixels) in a fundus image, so the ROC is insensitive to the change of specificity due to the large number of true negative, i.e. unlabeled non-bifurcation pixels. For better discriminability of ROC curve, all positive points can be weighed with a factor F larger than 1 by the following equation:

$$F = 2 \times \sqrt{\frac{\text{total No. of negative}}{\text{total No. of positive}}}$$

- [0072] In an aspect, introduction of factor F can enhance the influence of positive points so the ROC curve is more sensitive to changes of sensitivity and specificity. Assuming there are n images used in feature selection, the metric giving the AUC for the probability maps is outlined as follows:

- a) find the threshold values $v_0, v_1, v_2, \dots, v_k$ for all probability maps;
- b) for threshold value $i = v_0, \dots, v_k$
 1. threshold all probability maps and obtain thresholded images $mi_1, mi_2, \dots, mi_n$;
 2. compute TP, FP, TN and FN for $mi_1, mi_2, \dots, mi_n$;
 3. sum all TP, FP, TN and FN together for all thresholded images; and/or
 4. calculate the sensitivity and specificity for threshold value I ; and/or
- c) compute the AUC according to the pairs of sensitivity and specificity for all threshold values.

- [0073] As described in further detail below, one skilled in the art will appreciate that this is a functional description and that the respective functions can be performed by software, hardware, or a combination of software and hardware. A unit can be software, hardware, or a combination of software and hardware. The units can comprise the processing Software **606** as illustrated in **FIG. 6** and described below. In one exemplary aspect, the units can comprise a computer **601** as illustrated in **FIG. 6** and described below.

- [0074] **FIG. 6** is a block diagram illustrating an exemplary operating environment

for performing the disclosed methods. This exemplary operating environment is only an example of an operating environment and is not intended to suggest any limitation as to the scope of use or functionality of operating environment architecture. Neither should the operating environment be interpreted as having any dependency or requirement relating to any one or combination of components illustrated in the exemplary operating environment.

[0075] The present methods and systems can be operational with numerous other general purpose or special purpose computing system environments or configurations. Examples of well known computing systems, environments, and/or configurations that can be suitable for use with the systems and methods comprise, but are not limited to, personal computers, server computers, laptop devices, and multiprocessor systems. Additional examples comprise set top boxes, programmable consumer electronics, network PCs, minicomputers, mainframe computers, distributed computing environments that comprise any of the above systems or devices, and the like.

[0076] The processing of the disclosed methods and systems can be performed by software components. The disclosed systems and methods can be described in the general context of computer-executable instructions, such as program modules, being executed by one or more computers or other devices. Generally, program modules comprise computer code, routines, programs, objects, components, data structures, etc. that perform particular tasks or implement particular abstract data types. The disclosed methods can also be practiced in grid-based and distributed computing environments where tasks are performed by remote processing devices that are linked through a communications network. In a distributed computing environment, program modules can be located in both local and remote computer storage media including memory storage devices.

[0077] Further, one skilled in the art will appreciate that the systems and methods disclosed herein can be implemented via a general-purpose computing device in the form of a computer **601**. The components of the computer **601** can comprise, but are not limited to, one or more processors or processing units **603**, a system memory **612**, and a system bus **613** that couples various system components including the processor **603** to the system memory **612**. In the case of multiple processing units **603**, the system can utilize parallel computing.

[0078] The system bus **613** represents one or more of several possible types of bus structures, including a memory bus or memory controller, a peripheral bus, an accelerated graphics port, and a processor or local bus using any of a variety of bus architectures. By way of example, such architectures can comprise an Industry Standard Architecture (ISA) bus, a Micro Channel Architecture (MCA) bus, an Enhanced ISA (EISA) bus, a Video Electronics Standards Association (VESA) local bus, an Accelerated Graphics Port (AGP) bus, and a Peripheral Component Interconnects (PCI), a PCI-Express bus, a Personal Computer Memory Card Industry Association (PCMCIA), Universal Serial Bus (USB) and the like. The bus **613**, and all buses specified in this description can also be implemented over a wired or wireless network connection and each of the subsystems, including the processor **603**, a mass storage device **604**, an operating system **605**, processing software **606**, processing data **607**, a network adapter **608**, system memory **612**, an Input/Output Interface **610**, a display adapter **609**, a display device **611**, and a human machine interface **602**, can be contained within one or more remote computing devices **614a,b,c** at physically separate locations, connected through buses of this form, in effect implementing a fully distributed system.

[0079] The computer **601** typically comprises a variety of computer readable media. Exemplary readable media can be any available media that is accessible by the computer **601** and comprises, for example and not meant to be limiting, both volatile and non-volatile media, removable and non-removable media. The system memory **612** comprises computer readable media in the form of volatile memory, such as random access memory (RAM), and/or non-volatile memory, such as read only memory (ROM). The system memory **612** typically contains data such as processing data **607** and/or program modules such as operating system **605** and processing software **606** that are immediately accessible to and/or are presently operated on by the processing unit **603**.

[0080] In another aspect, the computer **601** can also comprise other removable/non-removable, volatile/non-volatile computer storage media. By way of example, **FIG. 6** illustrates a mass storage device **604** which can provide non-volatile storage of computer code, computer readable instructions, data structures, program modules, and other data for the computer **601**. For example and not meant to be limiting, a mass storage device **604** can be a hard disk, a removable magnetic disk, a removable

optical disk, magnetic cassettes or other magnetic storage devices, flash memory cards, CD-ROM, digital versatile disks (DVD) or other optical storage, random access memories (RAM), read only memories (ROM), electrically erasable programmable read-only memory (EEPROM), and the like.

[0081] Optionally, any number of program modules can be stored on the mass storage device **604**, including by way of example, an operating system **605** and processing software **606**. Each of the operating system **605** and processing software **606** (or some combination thereof) can comprise elements of the programming and the processing software **606**. Processing data **607** can also be stored on the mass storage device **604**. Processing data **607** can be stored in any of one or more databases known in the art. Examples of such databases comprise, DB2®, Microsoft® Access, Microsoft® SQL Server, Oracle®, MySQL, PostgreSQL, and the like. The databases can be centralized or distributed across multiple systems.

[0082] In another aspect, the user can enter commands and information into the computer **601** via an input device (not shown). Examples of such input devices comprise, but are not limited to, a keyboard, pointing device (*e.g.*, a “mouse”), a microphone, a joystick, a scanner, tactile input devices such as gloves, and other body coverings, and the like. These and other input devices can be connected to the processing unit **603** via a human machine interface **602** that is coupled to the system bus **613**, but can be connected by other interface and bus structures, such as a parallel port, game port, an IEEE 1394 Port (also known as a Firewire port), a serial port, or a universal serial bus (USB).

[0083] In yet another aspect, a display device **611** can also be connected to the system bus **613** via an interface, such as a display adapter **609**. It is contemplated that the computer **601** can have more than one display adapter **609** and the computer **601** can have more than one display device **611**. For example, a display device can be a monitor, an LCD (Liquid Crystal Display), or a projector. In addition to the display device **611**, other output peripheral devices can comprise components such as speakers (not shown) and a printer (not shown) which can be connected to the computer **601** via Input/Output Interface **610**. Any step and/or result of the methods can be output in any form to an output device. Such output can be any form of visual representation, including, but not limited to, textual, graphical, animation, audio, tactile, and the like.

[0084] The computer **601** can operate in a networked environment using logical connections to one or more remote computing devices **614a,b,c**. By way of example, a remote computing device can be a personal computer, portable computer, a server, a router, a network computer, a peer device or other common network node, and so on. Logical connections between the computer **601** and a remote computing device **614a,b,c** can be made via a local area network (LAN) and a general wide area network (WAN). Such network connections can be through a network adapter **608**. A network adapter **608** can be implemented in both wired and wireless environments. Such networking environments are conventional and commonplace in offices, enterprise-wide computer networks, intranets, and the Internet **615**.

[0085] For purposes of illustration, application programs and other executable program components such as the operating system **605** are illustrated herein as discrete blocks, although it is recognized that such programs and components reside at various times in different storage components of the computing device **601**, and are executed by the data processor(s) of the computer. An implementation of processing software **606** can be stored on or transmitted across some form of computer readable media. Any of the disclosed methods can be performed by computer readable instructions embodied on computer readable media. Computer readable media can be any available media that can be accessed by a computer. By way of example and not meant to be limiting, computer readable media can comprise “computer storage media” and “communications media.” “Computer storage media” comprise volatile and non-volatile, removable and non-removable media implemented in any methods or technology for storage of information such as computer readable instructions, data structures, program modules, or other data. Exemplary computer storage media comprises, but is not limited to, RAM, ROM, EEPROM, flash memory or other memory technology, CD-ROM, digital versatile disks (DVD) or other optical storage, magnetic cassettes, magnetic tape, magnetic disk storage or other magnetic storage devices, or any other medium which can be used to store the desired information and which can be accessed by a computer.

[0086] The methods and systems can employ Artificial Intelligence techniques such as machine learning and iterative learning. Examples of such techniques include, but are not limited to, expert systems, case based reasoning, Bayesian networks,

behavior based AI, neural networks, fuzzy systems, evolutionary computation (e.g. genetic algorithms), swarm intelligence (e.g. ant algorithms), and hybrid intelligent systems (e.g. Expert inference rules generated through a neural network or production rules from statistical learning).

[0087] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the scope of the methods and systems. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, numbers of samples, etc.), but some errors and deviations should be accounted for.

[0088] As an example, the disclosed methods and systems were applied to microaneurysm detection for DR screening and drusen detection for AMD detection. If not mentioned otherwise, the computations were performed in the green channel of fundus images.

[0089] **Microaneurysm detection**

[0090] The performance of the disclosed framework at detecting microaneurysms was first evaluated at a lesion level, on a set of 100 deidentified images manually segmented by a clinician expert (MDA). Twenty-six of these images were taken from a DR screening program in the Netherlands; these images were originally captured using a Canon CR5 nonmydriatic 3CCD camera at 45 degree field of view; and 74 were obtained from a retinal referral clinic; these images were captured using a Topcon TRC-50 at 45 degree field of view.

[0091] The size of the images is 768X576 pixels and the field of view is approximately 540 pixels in diameter. 55/100 of the images contained lesions. In these images, a total of 858 red lesions were identified.

[0092] Half of the images in this dataset were used for training and the other half for testing. In order to validate the optimal fitting of the filters to the reference samples, the optimal filtering framework (including confounders) was also compared to an approach where analytical filters are selected to maximize the classification accuracy, by cross-validation, on the set of reference samples ('training set'). The analytical filters used in this experiment were typical: Gaussian derivatives and Gabor wavelets in color opponency space. All other aspects of the method (convolution and

normalization of the data, k-NN classifier with the same risk) remained unchanged. The radius of the filters was set to 9 pixels for this application. The optimal filters are reported in **FIGS. 7A-7B**, wherein the upper row of each filter is convolved with vertical Haar filters dilated by a factor of 2 and the lower row of each filter is convolved with horizontal Haar filters dilated by a factor of 2. As an example, **FIGS. 7A-7B** illustrate that similar sets of filters can be obtained regardless of the method that is used to collect the set of reference samples.

[0093] In an aspect, **FIG. 8** illustrates an exemplary microaneurysm detection (e.g., detection image **804**) by the disclosed mathematical model based method in the macular region of a JPEG-compressed image **802** used in the EyeCheck screening program.

[0094] The free-response receiver-operating characteristic (FROC) curves of the different methods on the testing set are reported in **FIG. 9**, wherein the “Expert driven approach - no confounders” shows the performance obtained with a simplified version of the method where the confounder samples were not in the training set; there were only 2 reference samples: a small and a large typical lesion. “Data-driven approach – any negative samples” shows the performance obtained if the negative reference samples are selected at random outside of the manually segmented regions, instead of being selected among negative lesion confounders (i.e. among false positives of candidate selection). “Data-driven approach - no normalization” shows the performance obtained if the normalization step is omitted both for training and testing.

[0095] The time complexity assessment of the method is presented in **FIGS. 10A-10D**, wherein the computation times were obtained on a standard PC running at 2.26 GHz. Each vertex in **FIG. 10A** from left to right, corresponds to one curve in **FIG. 10B** from “299 samples” to “61373 samples.” Likewise, each vertex in **FIG. 10C** from left to right, corresponds to one curve in **FIG. 10D** from “5 PCSs” to “200 PCs.”

[0096] For convenience, the time complexity of the mathematical model based approach is studied (it is easier to increase the number of generated samples); similar computations times are obtained with the direct sampling approach.

[0097] Once the disclosed method was calibrated at a lesion level, the performance of the best performing version of the disclosed algorithm (the mathematical-model

approach) was compared at an examination level to a re-implementation of Niemeijer's method. This experiment was carried out on a set of images from the same screening program. The size of images and that of the field of view are similar to the previous set. 2,739 consecutive examinations from diabetic patients on their first visit were selected from a set of first visits in 2008. Each examination consists of two images per eye (a macula-centered and an optic disc centered image).

[0098] Sixty-seven of them were diagnosed with DR by a single retinal specialist, and the maximal microaneurysm presence risk measured within this set of four images was used as DR risk. The receiver-operating characteristic (ROC) of these two methods are reported in **FIG. 11**, wherein ROC of microaneurysm detection at an image level on a set of 2,739 patient images, including 67 with referable DR.

[0099] **Drusen detection**

[00100] In the second application of the disclosed framework, drusen are differentiated from Stargardt's disease flecks. Thus, the lesions and lesion confounders appear in different image sets, and the problem is to differentiate the two types of lesions as to whether the lesions are typical for AMD (drusen) or Stargardt's disease (flecks). A set of 15 images of patients with AMD, all containing drusen, as confirmed by a clinician expert (MDA), and 15 images containing flecks as confirmed to have Stargardt's disease by positive genetic testing for the ABCA4 haplotype were selected. Images were acquired with a Zeiss FF3 30-degree camera and recorded on Kodachrome film (ASA 100). Film-based images were scanned at 3456 x 2304 pixels, 12 bit depth, using a 3 color channel CCD scanner.

[00101] A set of 300 drusen and 300 flecks were manually annotated in these images and used as reference samples for the sampling approach. A leave-one-image-out cross-validation was performed to assess the sampling approach. To validate the mathematical model approach, the 600 samples were used as a testing set. The radius of the filters was set to 13 pixels for this application. The optimal filters are reported in **FIGS. 7C-7D**. The ROC-s are reported in **FIG. 12**.

[00102] Accordingly, an optimal filter framework for detecting objects in retinal images has been provided. The framework can comprise a design of a set of filters optimally representing the typical target lesions, as well as the negative lesion confounders, e.g. lesions that are similar looking but not the target lesions, and the positive lesion confounders, e.g. lesions that are easily missed because the lesions

have specific properties that are substantially different from the standard case. In order to design the optimal filter set, image samples representative of the three types of lesions are collected and the filters are defined as the principal components of these samples.

[00103] In one aspect, the disclosed methods and systems can ensure the representativeness of the reference image samples. Two completely different approaches for obtaining these maximally representative samples are disclosed and compared: an expert and a data-driven approach. The optimal filter set is used as a reference to classify new image samples. Because the feature space spanned by these filters is compact, the classification procedure, based on an approximate nearest neighbor search, is fast. This property can be relevant in medical applications such as the instantaneous assessment of retinal diseases.

[00104] The optimal filter framework has been tested on the detection of two important lesions in eye disease: microaneurysms and drusen. The results show that the detection performance achieved by the provided optimal filter framework is comparable to that of previous algorithms presented, however the new method is much faster: each retinal image is processed in less than a second, as opposed to several minutes with the prior approaches. This implies that instantaneous assessment of retinal images for DR is achievable, while maintaining the performance achieved by previously published algorithms. The results show that the optimal filter framework also has good performance in the differentiation of drusen from Stargardt's disease flecks, illustrating its generality.

[00105] The optimal filter sets obtained varied little with the method through which the optimal filter sets were obtained. In other words, it mattered little whether the representative samples (from which the optimal filters are derived) are obtained from a mathematical model designed by a non-clinician domain expert, i.e. expert driven, or by directly sampling a representative set of images at locations annotated by one or more expert clinicians, i.e. data-driven, following the sampling procedure described herein. Thus, an optimal filter framework, with the set of domain optimal filters obtained directly from image samples, and only relying on an expert clinician input for annotating, performs close (for DR detection) or equivalent (for drusen versus flecks differentiation) to a system in which the filters require the design of a model by a non-clinician expert. The data-driven approach is expected to generalize

well to other retinal image analysis problems, and possibly, to other medical image analysis problems, because only limited clinician expert annotation effort is required, and no further domain knowledge is required on the designer of the framework. Its generality and lack of bias is illustrated also by the fact that incorporating color into the representative samples results in equal or superior performance compared to samples from a specific color channel, (e.g., the green channel, which is known by domain experts to be more discriminant). If the expert modeler had been biased and assumed that color was irrelevant, and therefore did not incorporate color into their mathematical model, that might have unnecessarily limited the performance. For the data-driven form of the optimal filter framework there is no need to exclude potentially irrelevant color channels a priori. The expert-driven approach was superior to the data-driven approach when the designer of the mathematical models had sound non-clinician expert knowledge (e.g., microaneurysm detection). It shows that, if expert knowledge is available, it is possible to push performance further through mathematical modeling. Moreover, should the method be applied to a new dataset, the value of a few parameters could be changed, while in the data-driven approach additional annotation might have been required.

[00106] Finally, the results indicate that using a set of filters obtained from factorial coding of the data - in this case, PCA – may be superior, and at least equal, to the set of filters obtained through feature selection on a Gaussian derivative or Gabor wavelet or filterbank. As an example, from all of the potential filter sets in the filter, or feature, space, a small set Gabor or Gaussian derivative filters may be optimal, but that for specific object detection problems, a locally optimal, better performing filter set exists, and can be found in this space through the framework described herein.

[00107] **Bifurcation Detection**

[00108] In an exemplary experiment, a total of 80 de-identified retinal color images from 80 subjects from a diabetic retinopathy screening program in the Netherlands were created by registration of 2 separate images per patients. The size of images was approximately 800X650 pixels in JPEG format. The number of images in a first training set was 50, and the number of images in a second training set was 10. The number of test images was 20. To build and evaluate a vision system or vision

machine, an expert annotated a set of centers of bifurcations in the training sets and test images and a retinal specialist reviewed these annotations for correctness. After annotation, all bifurcation were samples at a scale σ of 25X25 pixels. In the training stage, 10 bifurcations were randomly sampled per image so 500 samples are created, and rotating the samples resulted in 4000 samples. PCA was applied separately on the samples in red, blue and green channels. In an aspect, images in red channels contain the most amount of information and least amount of noise because the cumulative variance(CV) curve of the red channel image rises most rapidly.

[00109] As an example, the information of bifurcation samples are concentrated in the first few number of PCs. Thus the first 30 PCs of red and green channels can be selected respectively for feature selection. For the negative points, 2000 non-bifurcations are selected from each training image so there will be 100000 negative points in the feature space. This number is chosen in the consideration that the ratio of true bifurcation and true non-bifurcation is very large, accordingly, a large amount of negative points can be selected to simulate this situation.

[00110] In the feature selection step, the maximal number of optimal filters is set to be 10. The distance D that defines the region of true bifurcation is the square root of 41. In this case the 10 most discriminative filters are 6th PC in red, and 2nd, 3rd, 4th, 5th, 6th, 7th, 18th and 19th PCs in green channels. It is worth noticing that the selected filters depends on the distribution of the reference points and since the negative points are randomly sampled for different reference points feature selection might give different results.

[00111] Using these 10 filters, a 10-dimensional feature space was established, within which there are 4000 positive points and 100000 negative points. A k-NN algorithm was used to classify 20 test images with $K = 33$. The metric used to evaluate the results of the 20 test images was the same as in feature selection. The overall AUC was 0.883.

[00112] The results show that a vision machine based retinal bifurcation detection method can be developed based solely on a limited number of expert annotated retinal images with exemplar branching points. The results also show that detection performance of the system, compared to a human expert, on a different dataset, as measured by AUC, is satisfactory.

[00113] In an aspect, using a vision machine approach as described herein, an

automated retinal vessel bifurcation detection system, based on very limited expert contribution. The vision machine, systems and methods described herein can be more widely used to develop simple object search systems for similar applications.

[00114] In an aspect, similar approaches (e.g., optimal filter or vision machine) can be used to create detection systems for various objects of interest. As an example, the systems and methods described herein can be used to detect apples in images of orchards, helicopter landing pads in high altitude reconnaissance images, and cell nuclei in phase contrast images of mitotic fibroblasts. Other images and objects of interest can be processed. As a further example, the methods described herein can be highly general but can be trained to be highly specific in a specific domain. Any domain can be used and the systems and methods can be trained for any particular object of interest.

[00115] In an aspect, methods are disclosed for identifying an object of interest in a plurality of digital images (e.g., ImageORG), where each of these images comprises a plurality of wavelength bands, and each ImageORG comprises a plurality of raw images that were combined into a single ImageORG. As an example, the methods can comprise obtaining first samples of the intensity distribution of the object of interest in one or more wavelength bands, obtaining second samples of the intensity distribution of confounder objects, at a frequency high enough to affect a performance metric, transforming the first and second samples into an appropriate space, thereby creating Imagetrans, performing dimension reduction on the transformed first and second samples altogether, whereby the dimension reduction of the transformed first and second samples creates an object detector, transforming ImageORG into the appropriate space to obtain Imagetrans, projecting Imagetrans into the space of reduced dimension to obtain Imagereduc, classifying each pixel p in Imagereduc with an appropriate neighborhood N_p , based on a comparison with the samples obtained, and automatically identifying an object of interest from the abnormal pixels.

[00116] In one aspect, provided is a general, optimal filter framework for the detection of lesions in retinal images, derived through factor analysis of the lesions and their confounders. This optimal filter framework can be applied to other lesion detection problems in retinal images, where rapid system development and instantaneous performance are required.

- [00117] Bifurcations of retinal vessels are of great interest in image processing algorithms such as registration, segmentation and change detection. In one aspect, a method for direct bifurcation detection based on the optimal filter framework can be performed. For example, a set of filters can be generated representing all cases of bifurcations. These filters can be used to generate a feature space for a classifier to distinguish bifurcations and non-bifurcations. This approach can use a minimal number of assumptions, and thus can be based upon training images and expert annotations of bifurcations. For example, the method can comprise training on 60 fundus images and testing on 20 fundus images. Example results can comprise an AUC of 0.883, demonstrating that the method can compare well to a human expert.
- [00118] The analysis of retinal vessel bifurcations can help monitor and diagnose retinopathies such as vessel occlusion, hypertension and/or diabetes. Retinal vessel bifurcations are also important structures for vessel segmentation and analysis of the retinal vessel trees and usually used as landmarks for image registration because of the geometrical stability of the vessel bifurcations. Much work has been done for detection of bifurcations so far. However, most of these approaches use the geometrical and topological information of the vessel tree to detect bifurcations and the successful detection depends on the quality of the underlying vessel segmentation algorithm.
- [00119] In one aspect, the methods of the present disclosure contemplate an optimal filter framework comprising a formalized image analysis approach that allows an unbiased, almost parameterless automated system for object-background separation. For example, the filter framework can build an object (e.g., vessel bifurcation) detector based on a limited number of expert-marked exemplar objects. This approach is optimal in comparison to model-based and filterbank-based approaches for the separation of object and background.
- [00120] To illustrate aspects of the disclosure, an example study is described below in which a retinal bifurcation detection method is developed using the optimal filter framework on a limited number of expert-annotated retinal image, and the example retinal bifurcation detection method is evaluated by comparison to a human expert.
- [00121] **FIG. 13A** illustrates an overview of an exemplary filter framework comprising two stages. **FIG. 13B** illustrates an example fundus image with annotated bifurcations labeled by dark circles. **FIG. 13C** illustrates bifurcation

samples (1st column), and in red (2nd column), green (3rd column) and blue (4th column) channels. In one aspect, the optimal filter framework can consist of a training and a test stage as shown in **FIG. 13A**. During the training stage, a set of fundus images S with expert-annotated bifurcations, indicated as in **Fig. 13B**, can be used to build a set of optimal filters and to optimize the classification. Internally, a training set S can be divided into two sets, $S1$ and $S2$. $S1$ can be used to build the filter set F , while $S2$ can be used to perform feature selection on F , resulting in selected filters F' , from which the feature space can be formed and reference points can be generated. Then, a classifier can be trained to detect bifurcations for a fundus image in terms of generating a soft-labeled map indicating the probability of every pixel to be a bifurcation. During the test stage, a probability map can be generated for every test image in T , and the performance can be evaluated and compared to the ground truth. To maintain generality and robustness, $S1$, $S2$ and T can comprise representative images from the real data that are kept entirely separated. The following parts discuss the details of the optimal filter framework, including the sample generation, filter generation, bifurcation detection, feature selection, and the evaluation metric.

[00122] In one aspect, methods can comprise generating samples. For example, methods can comprise annotating the center of bifurcations in $S1$ and $S2$ to obtain bifurcation samples as subimages at a specific scale σ (measured in pixels). To achieve rotation invariance, each sample can be rotated, for example, by 0 degrees, 45 degrees, 90 degrees, 135 degrees, 180 degrees, 225 degrees, 270 degrees, and 315 degrees. In preliminary studies, there was no advantage in using a higher number of orientations, though results may differ if the scales of the samples are different. To obtain a consistent sample image pattern, a circular mask can be superimposed on the rotated sample image to generate circular samples. In addition, the sample images can be decomposed into red, green and blue channels (**FIG. 13C**), and samples in these channels can be considered as independent sample sets.

[00123] In one aspect, methods can comprise generating filters. For example, methods can use principal component analysis (PCA) to generate the feature space. PCA can comprise an orthogonal transformation converting the original data into a new coordinate system so that the features are represented by a number of linearly uncorrelated variables called principal components (PCs). In one aspect, every

sample of subimage can be a single observation. Additionally, by applying PCA on the samples set, PCs can be obtained representing any instance of that sample set. In one aspect, the first few PCs can account for the majority variance of the original data. If the first M PCs are retained such that the cumulative variance (CV) of the PCs are the majority of the total variance, the first M PCs can be used to approximate any instance of bifurcations. Thus, according to such accuracy, the PCs can be selected as the optimal filters.

[00124] For example, the first component extracted in a principal component analysis can account for a maximal amount of total variance in the observed variables. Under typical conditions, this means that the first component can be correlated with at least some of the observed variables. It may be correlated with many. The second component extracted can have two important characteristics. First, this component can account for a maximal amount of variance in the data set that was not accounted for by the first component. Again under typical conditions, this means that the second component can be correlated with some of the observed variables that did not display strong correlations with component 1. The second characteristic of the second component is that it can be uncorrelated with the first component. Literally, if one were to compute the correlation between components 1 and 2, that correlation would be zero. The remaining components that are extracted in the analysis can display the same two characteristics: each component accounts for a maximal amount of variance in the observed variables that was not accounted for by the preceding components, and is uncorrelated with all of the preceding components. A principal component analysis proceeds in this fashion, with each new component accounting for progressively smaller and smaller amounts of variance (this is why only the first few components are usually retained and interpreted). When the analysis is complete, the resulting components can display varying degrees of correlation with the observed variables, but can be completely uncorrelated with one another.

[00125] Samples from S1 can be projected into the initial feature space by convolving them with these optimal filters for later usage. In particular, bifurcation samples in training set S1 can be projected into the feature space to form the positive reference points. Likewise, non-bifurcations can be randomly sampled in S1 and projected into the feature space to form the negative reference points. While all

features can be computed here, in the trained algorithm, this computation can be performed with those filters that span the final, low-dimension feature space, which results from the feature selection described below.

- [00126] In one aspect, the methods can comprise performing bifurcation detection. After the feature space is generated with reference points, a classifier can be trained for the detection of bifurcations. For example, an image under detection can be transferred into the feature space by being convolved with filters so each pixel corresponds to a query point. In one aspect, the K-Nearest Neighbor algorithm (k-NN) or variation thereof can be used to classify these query points. Soft classification can be applied so the probability of the query point P to be a bifurcation is n/k , where k is the number of neighbors considered and n is the number of positive points among these neighbors.
- [00127] In one aspect, the methods can comprise performing feature selection. The dimension of the feature space can comprise the number of filters (e.g., PCs). In one aspect, the feature space is a high-dimension space. The feature space can be defined by the set of optimal filters, and thus, the features and filters can be interchangeable. Thus, for efficiency, feature selection can be applied to lower the dimension. In one aspect, feature selection can comprise a Sequential Forward Selection (SFS) algorithm or variation thereof. For example, the SFS can start with a candidate feature pool and, for each iteration, select out the best remaining feature according to a criterion, until a maximum number of features is reached or the criterion value starts to decline. Training set S2 can be used to generate the probability maps using algorithms of feature selection described above. In one aspect, probability maps can be generated with selected filters every iteration. The criterion to guide the selection can comprise the AUC for the ROC curve for the whole set of probability maps explained below.
- [00128] In one aspect, the methods can be evaluated according to an evaluation metric. An example metric to give the AUC can be pixel-based. For example, a bifurcation region can be defined with radius of R centered at every annotated bifurcation pixel. Every pixel of a binary image obtained by thresholding a probability map can be decided as true positive (TP), false positive (FP), true negative (TN) or false negative (FN) depending on whether the pixel falls within bifurcation regions or outside. For n test images, n probability maps can be

generated with the selected filters. The n probability maps can be thresholded with different values to generate different pairs of specificities and sensitivities. Then, the overall ROC can be plotted, and the AUC can be calculated.

[00129] In some implementations, the data can be highly skewed when the number of bifurcation pixels are small compared to a whole image. In such cases, the ROC can be insensitive to the change of specificity. For better discriminability of ROC, positive points can be weighed with a self-defined factor F larger than 1, thereby enhancing the influence of positive points so the ROC curve is more sensitive to changes of sensitivity and specificity.

[00130] To further illustrate the methods, exemplary data and results of the method are discussed. In one example, the data can comprise 80 fundus images created by registration of one image pair as described in herein. In the example data, the size of images can be about 800×650 pixels in JPEG format. The numbers of images in S1, S2 and T can comprise 50, 10 and 20 respectively. To build and evaluate this method, the centers of bifurcations can be manually annotated and a retinal specialist can review the annotations for correctness.

[00131] Bifurcation can be sampled at a scale σ of 25×25 pixels. In the training stage, 10 bifurcations can be randomly sampled per image so that 500 samples are created. Rotating these 500 samples can result in 4000 samples in total. **FIG. 14** illustrates example filters based on the example data. Specifically, **FIG. 14** shows the first 12 filters in three channels (e.g., first row is red channel, second row is green channel, and third row is blue channel) based on the example data. **FIG. 15** is an example plot of the cumulative variance (CV) of three channels (e.g., red, green, and blue) with respect to the number of PCs. As illustrated in **FIG. 15**, the lowest CV (e.g., representing the blue channel) has a slower increase compared two higher CVs (e.g., the highest representing the red channel, and the second highest representing the green channel). The slower increase of the blue channel can be explained by the fact that the blue channel comprises little information but noise. Thus, the first 30 PCs of red and green channels can be selected for feature selection.

[00132] In one aspect, non-bifurcations of 2000 can be randomly selected per training image, generating a total of 100000 negative points. Ten filters can be selected after the feature selection to build a 10-D feature space. The radius R of the bifurcation region can be the square root of 41 according to the vessel width in images. In one

aspect, an Approximate Nearest Neighbor (ANN) algorithm can be used to accelerate the k-NN classifier algorithm, which can be used to test on images in T with $k = 33$. As an illustration of example data, the AUC can be 0.883. **FIG. 16A** illustrates an AUC curve of test images with 10 selected features. **FIG. 16B** illustrates an example probability map of example data and **FIG. 16C** illustrates vein bifurcations detected by the methods described herein. Specifically, **FIG. 16C** illustrates a binary map overlapped with the original image used an example data. Bifurcations are labeled with circles, and white pixels are TPs, and black pixels are FPs. These figures indicate that this method finds most of the bifurcations. Most of false positives occurred within and near the optic disc.

[00133] In summary, the methods can comprise an optimal filter-based retinal bifurcation detection method. The optimal filter-based retinal bifurcation detection method can be based on a limited number of annotated retinal images with exemplar branching samples. Compared to other methods, this approach requires little morphological information about the target, and has few parameters: the scale σ of the sample, the numbers of positive samples and negative samples, and a classifier. Furthermore, the parameter scale σ might be eliminated in a multiscale approach. In conclusion, using the optimal filter framework, the methods can be implemented in an automated retinal vessel bifurcation detection system, based on very limited expert contribution. This method is tested on 20 fundus images, resulting in a general AUC of ROC curve 0.883, which is satisfactory compared to a human expert.

[00134] **FIG. 17** is a flowchart illustrating an exemplary method of analyzing an image. In step **1702**, at least one image having one or more annotations indicating a feature can be received. In one aspect, the feature can comprise a bifurcation. For example, the feature can comprise a blood vessel bifurcation. Additionally, the at least one image can comprise one or more fundus images. In step **1704**, training images can be generating from the at least one image. For example, each training image can be based on a respective section of the at least one image. The training images can comprise positive images having the feature and negative images without the feature. Furthermore, in step **1704**, one or more of the respective sections of the at least one image can be reproduced as a plurality of images rotated at different angles.

- [00135] In step **1706**, a feature space can be generated based on the positive images and the negative images. For example, one or more orthogonal filters can be generated from the positive and the negative images. In one aspect, each of the one or more orthogonal filters comprise an image based on one or more aspects indicative of at least one of the positive images or the negative images. As another example, optimal filters can be generated from the positive images and the negative images. The optimal filters can comprise the highest ranked filters according to each filter's relevance in identifying the one or more features. In one aspect, the optimal filters can be generated by performing a Sequential Forward Selection algorithm.
- [00136] In an aspect, the feature can be identified in one or more unclassified images based upon the feature space. For example, each pixel of the one or more unclassified images can be classified based on a K-Nearest Neighbor algorithm. In a further aspect, a probability image can be generated. The probability image can comprise probability pixels. In one aspect, each of the probability pixels can indicate a respective probability that a corresponding classified pixel indicates the feature.
- [00137] In an aspect, illustrated in **FIG. 18**, provided are methods of analyzing an image, comprising receiving an image at **1802**, transferring the image into a feature space at **1804**, and classifying one or more objects of interest in the transferred image as a bifurcation at **1806**.
- [00138] The image can comprise one or more fundus images. The methods can further comprise applying principal component analysis to a plurality of training images to generate a filter set that defines the feature space. The methods can still further comprise generating the feature space with one or more positive reference points and one or more negative reference points.
- [00139] The filter set can comprise a plurality of principal components wherein the plurality of principal components comprise a cumulative variance exceeds a threshold. Transferring the image into a feature space can comprise convolving the image with filters so each pixel of the image corresponds to a query point in the feature space. Classifying one or more objects of interest in the transferred image as a bifurcation can comprise applying a classifier trained for the detection of bifurcations.
- [00140] The methods can further comprise generating a probability image comprising

probability pixels, wherein each of the probability pixels indicating a respective probability that a corresponding classified pixel indicates the one or more objects of interest.

[00141] While the methods and systems have been described in connection with preferred embodiments and specific examples, it is not intended that the scope be limited to the particular embodiments set forth, as the embodiments herein are intended in all respects to be illustrative rather than restrictive.

[00142] Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; the number or type of embodiments described in the specification.

[00143] It will be apparent to those skilled in the art that various modifications and variations can be made without departing from the scope or spirit. Other embodiments will be apparent to those skilled in the art from consideration of the specification and practice disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit being indicated by the following claims.

CLAIMS

What is claimed is:

1. A method of analyzing an image, comprising:
receiving at least one image having one or more annotations indicating a feature;
generating training images from the at least one image, wherein each training image is based on a respective section of the at least one image, the training images comprising positive images having the feature and negative images without the feature; and
generating a feature space based on the positive images and the negative images.
2. The method of claim 1, wherein the feature comprises a blood vessel bifurcation.
3. The method of claim 1, wherein the at least one image comprises one or more fundus images.
4. The method of claim 1, wherein generating the training images comprises reproducing one or more of the respective sections of the at least one image as a plurality of images rotated at different angles.
5. The method of claim 1, wherein generating the feature space comprises generating one or more orthogonal filters from the positive and the negative images.
6. The method of claim 5, wherein each of the one or more orthogonal filters comprise an image based on one or more aspects indicative of at least one of the positive images or the negative images.
7. The method of claim 1, wherein generating the feature space comprises generating optimal filters from the positive images and the negative images,

the optimal filters comprising the highest ranked filters according to each filter's relevance in identifying the one or more features.

8. The method of claim 7, wherein generating the optimal filters comprises performing a Sequential Forward Selection algorithm.
9. The method of claim 1, further comprising identifying the feature in one or more unclassified images based upon the feature space.
10. The method of claim 9, wherein identifying the feature comprises classifying each pixel of the one or more unclassified images based on a K-Nearest Neighbor algorithm.
11. The method of claim 10, further comprising generating a probability image comprising probability pixels, wherein each of the probability pixels indicating a respective probability that a corresponding classified pixel indicates the feature.
12. A method of analyzing an image, comprising:
 - receiving an image;
 - transferring the image into a feature space; and
 - classifying one or more objects of interest in the transferred image as a bifurcation.
13. The method of claim 12, wherein the image comprises one or more fundus images.
14. The method of claim 12, further comprising applying principal component analysis to a plurality of training images to generate a filter set that defines the feature space.
15. The method of claim 14, further comprising generating the feature space with one or more positive reference points and one or more negative reference points.

16. The method of claim 14, wherein the filter set comprises a plurality of principal components wherein the plurality of principal components comprise a cumulative variance exceeds a threshold.
17. The method of claim 12, wherein transferring the image into a feature space comprises convolving the image with filters so each pixel of the image corresponds to a query point in the feature space.
18. The method of claim 12, wherein classifying one or more objects of interest in the transferred image as a bifurcation comprises applying a classifier trained for the detection of bifurcations.
19. The method of claim 18, further comprising generating a probability image comprising probability pixels, wherein each of the probability pixels indicating a respective probability that a corresponding classified pixel indicates the one or more objects of interest.
20. A system for analyzing an image, comprising:
 - a memory; and
 - a processor, coupled to the memory, wherein the processor is configured for,
 - receiving at least one image having one or more annotations indicating a feature;
 - generating training images from the at least one image, wherein each training image is based on a respective section of the at least one image, the training images comprising positive images having the feature and negative images without the feature; and
 - generating a feature space based on the positive images and the negative images.
21. A system for analyzing an image, comprising:
 - a memory; and

a processor, coupled to the memory, wherein the processor is configured for,
receiving an image,
transferring the image into a feature space, and
classifying one or more objects of interest in the transferred image as a bifurcation.

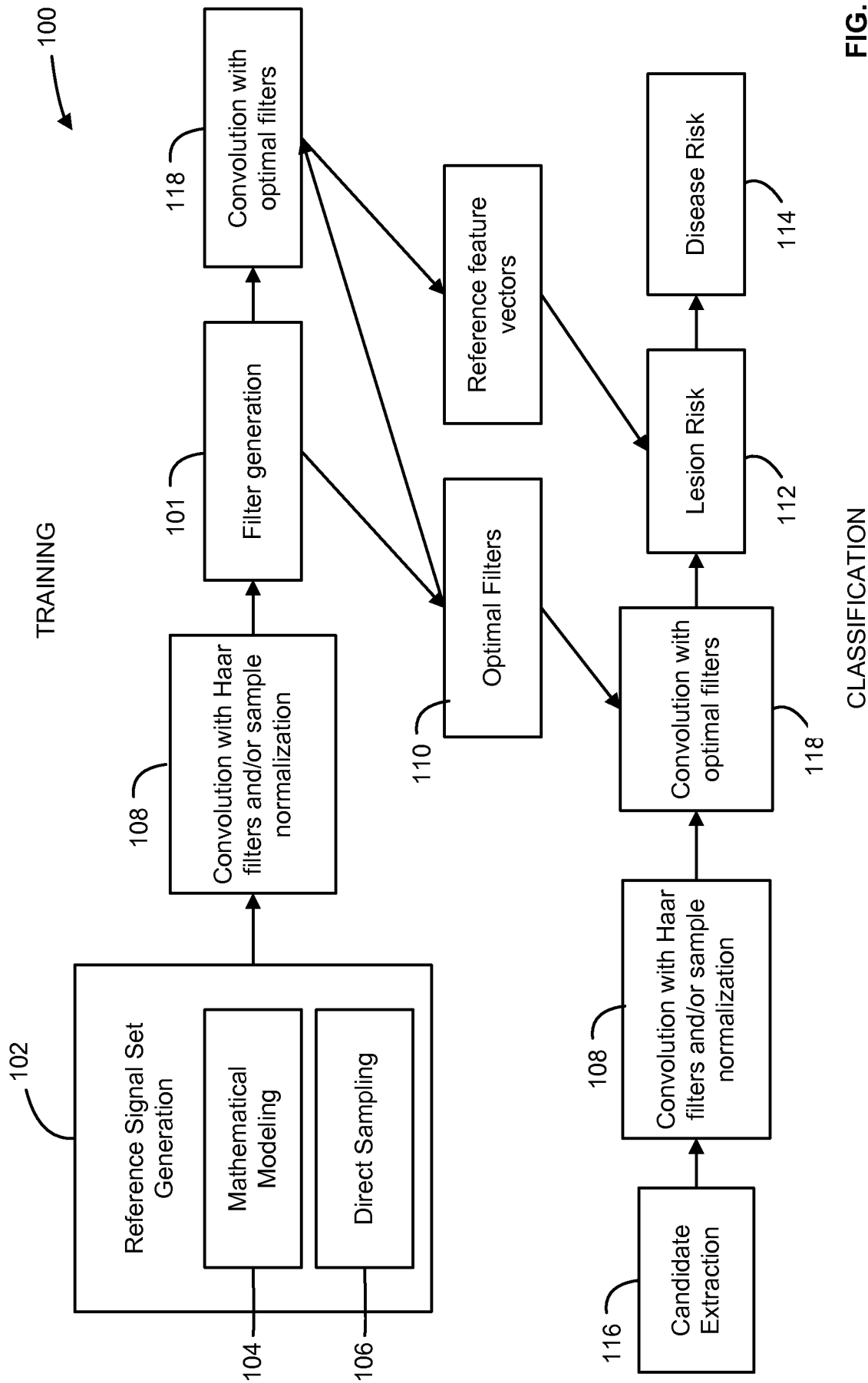


FIG. 1

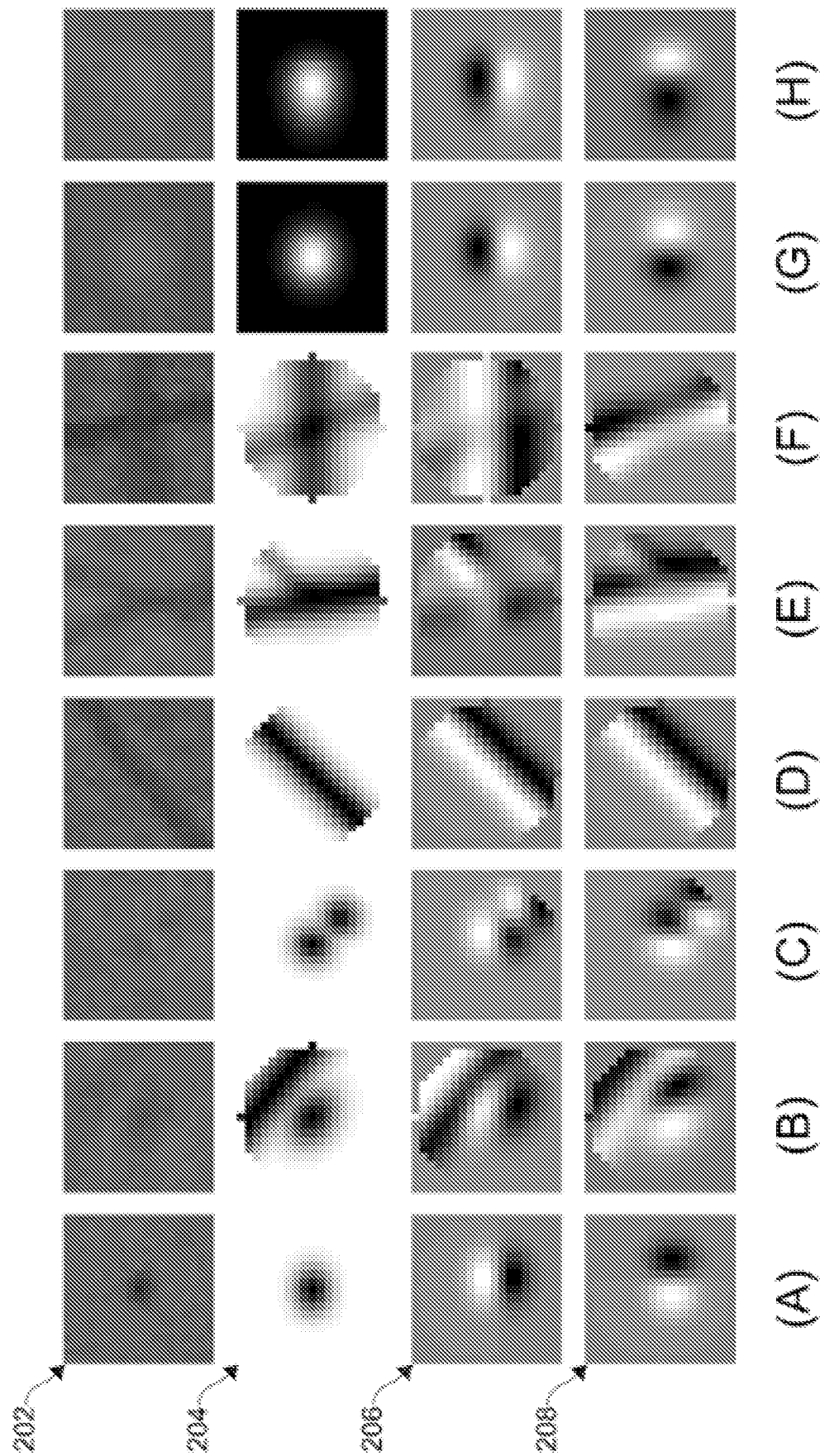


FIG. 2

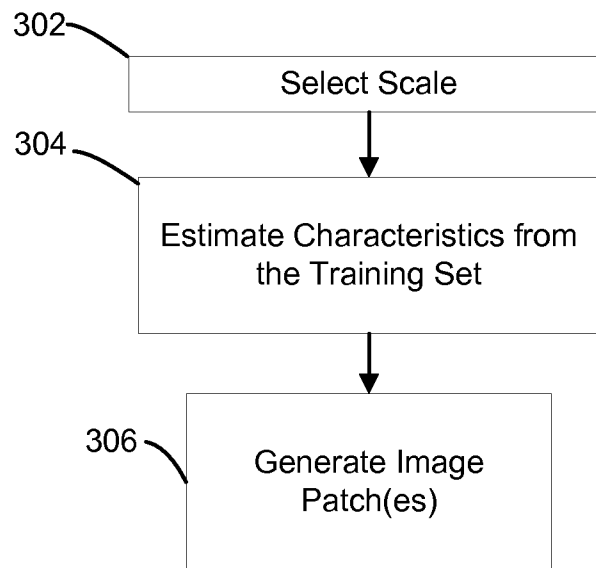


FIG. 3

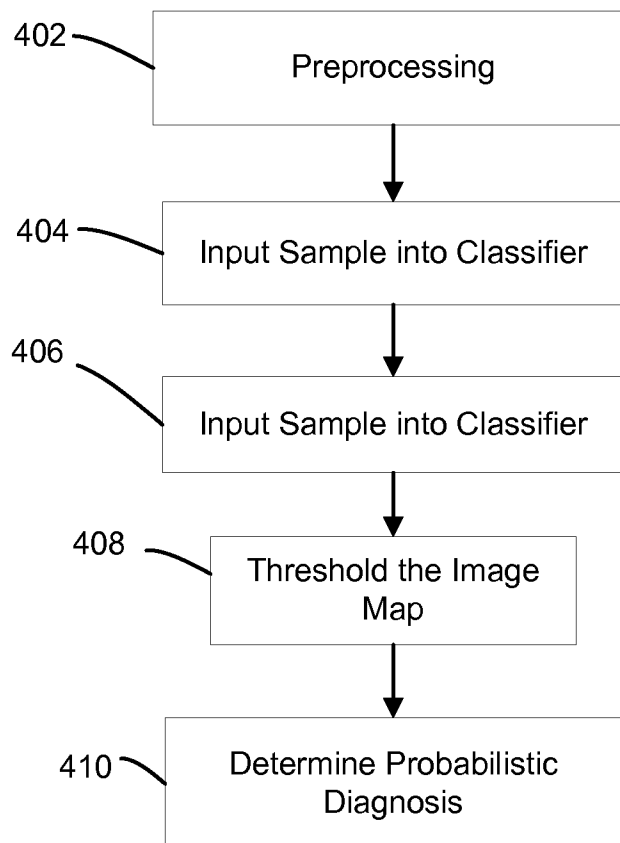
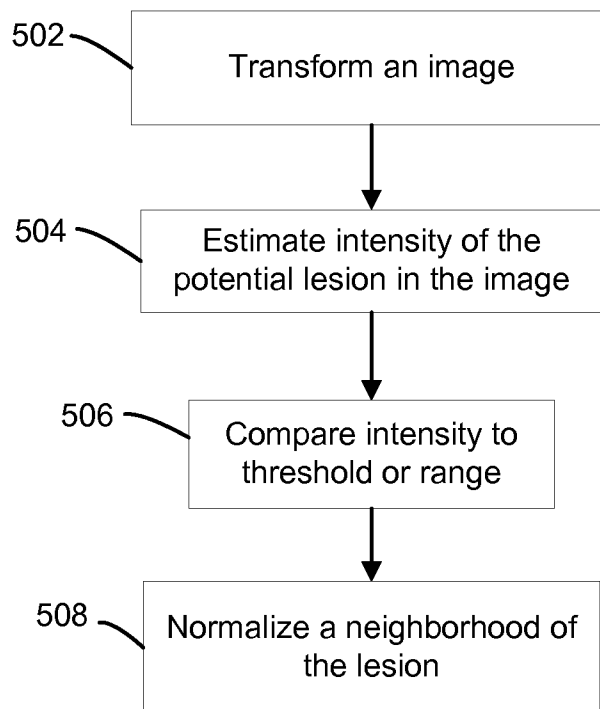


FIG. 4

**FIG. 5**

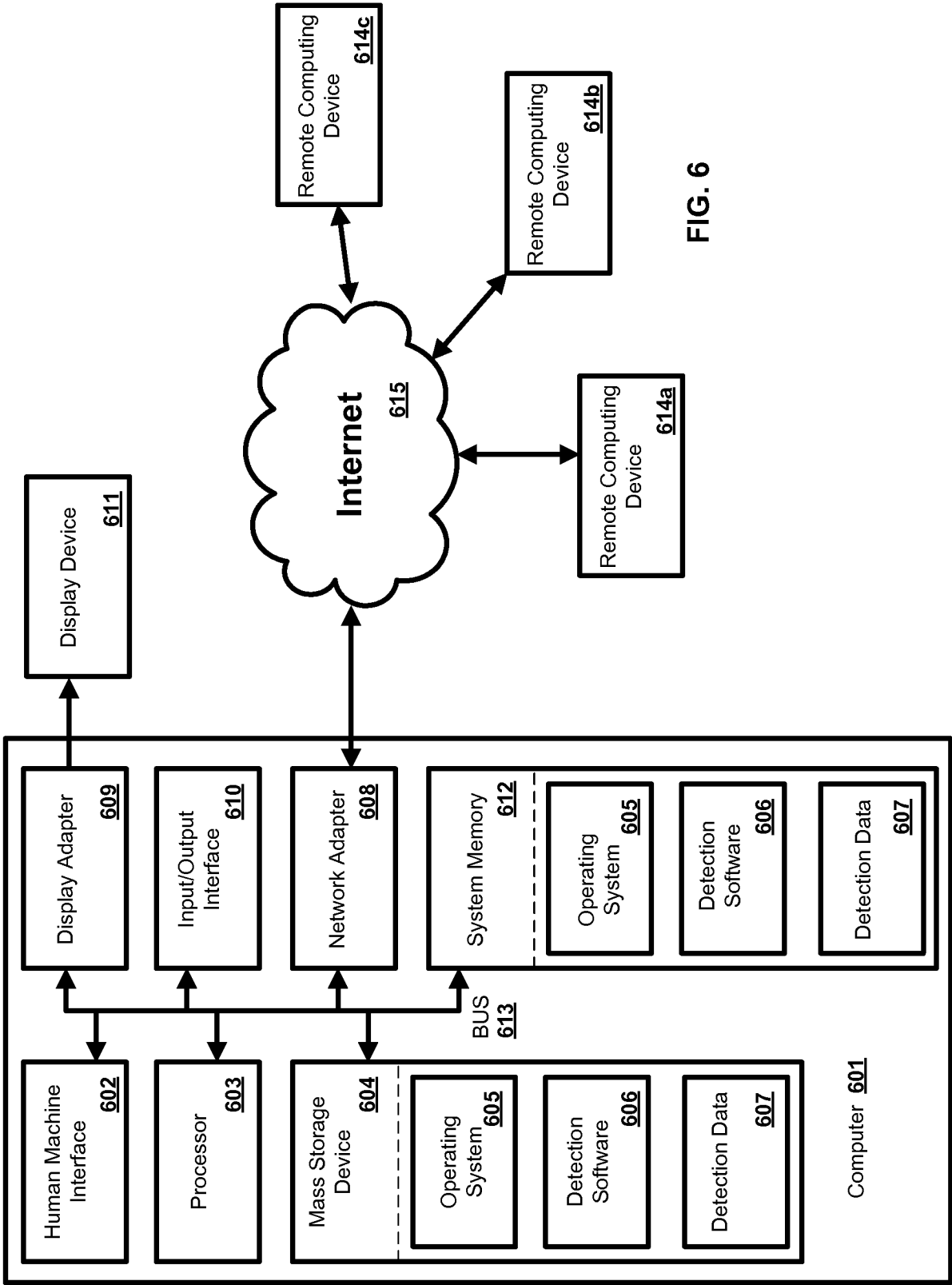


FIG. 6

MA-mathematical model approach

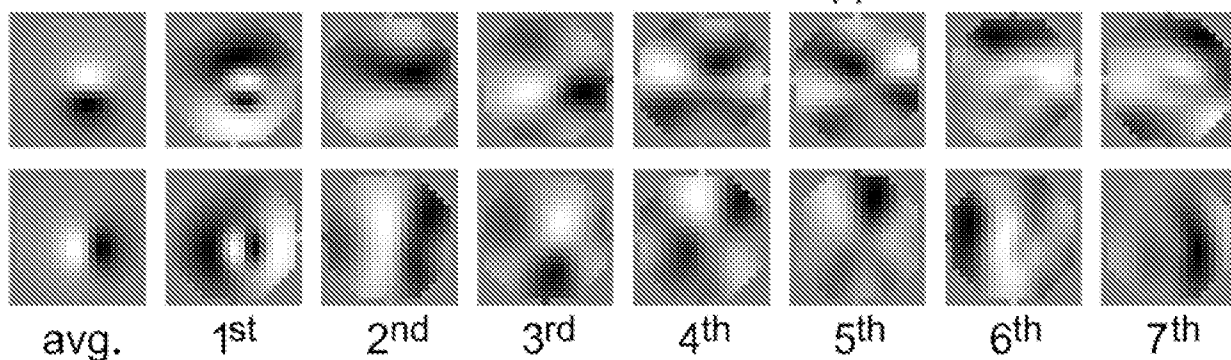


FIG. 7A

MA-sampling approach

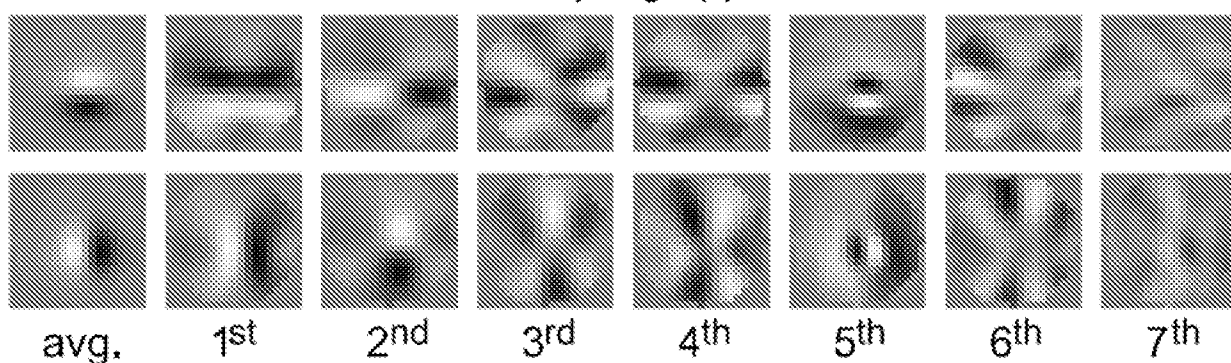


FIG. 7B

drusen-mathematical model approach

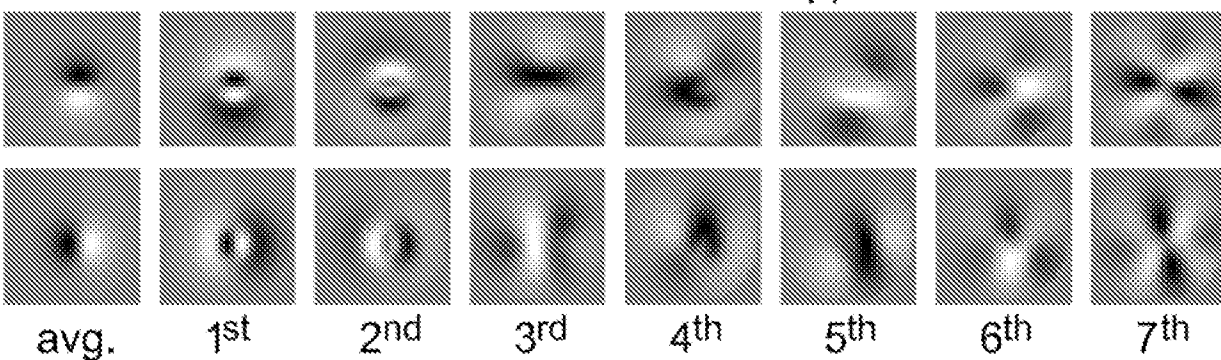


FIG. 7C

drusen-sampling approach

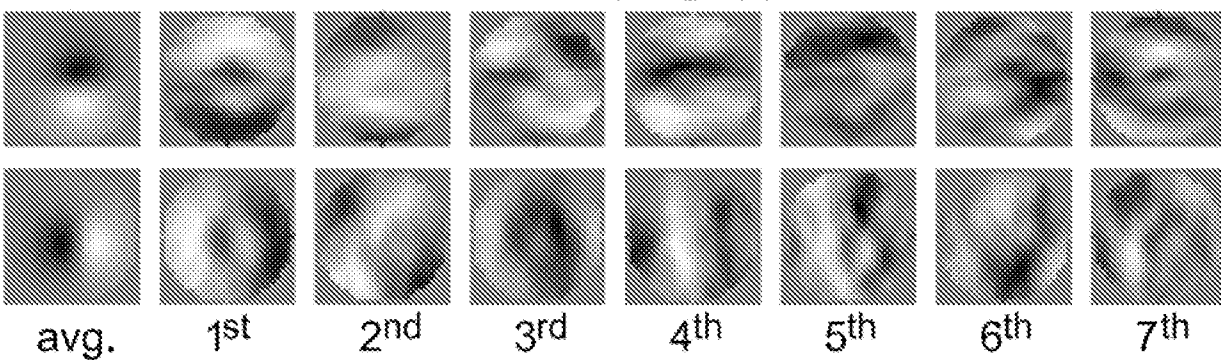


FIG. 7D

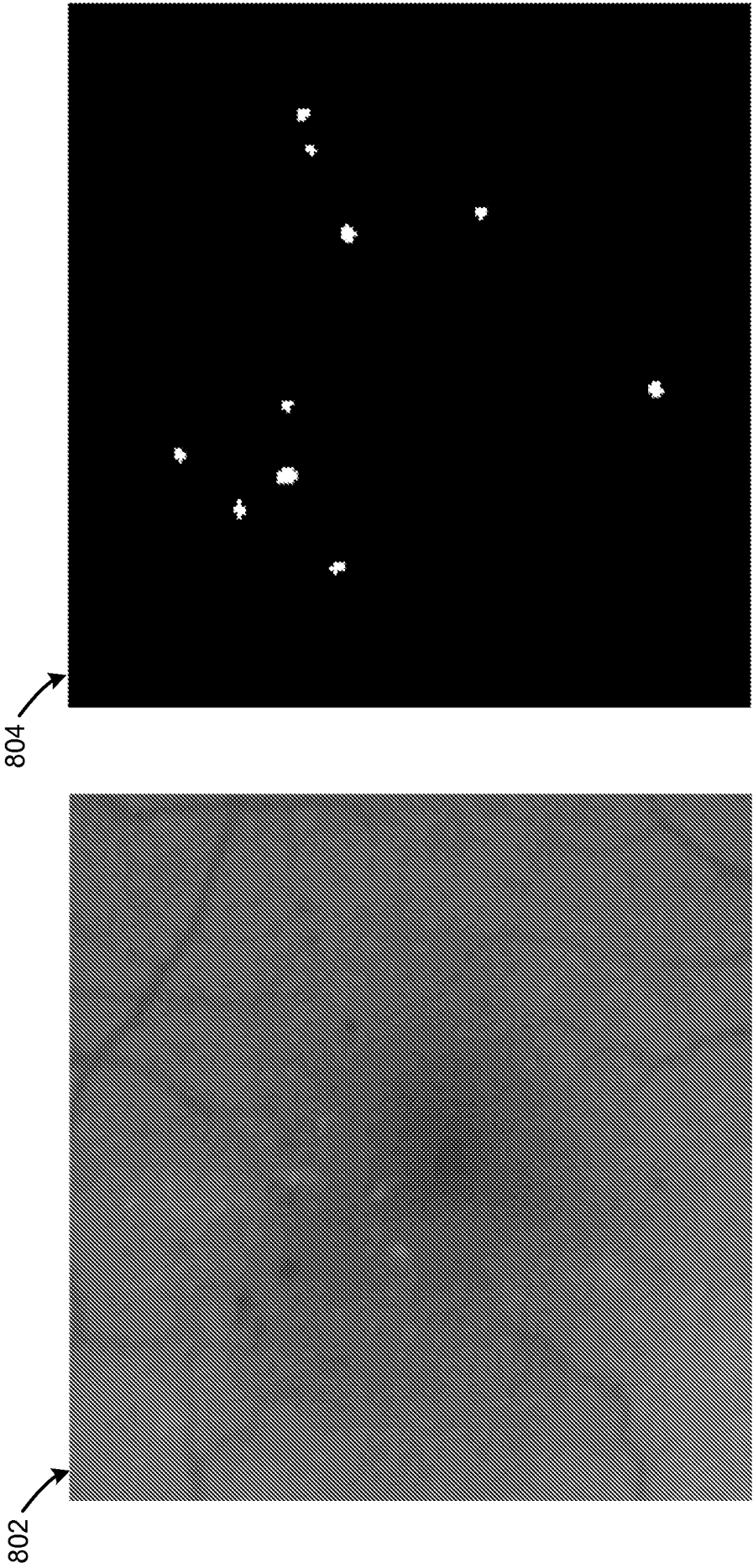


FIG. 8

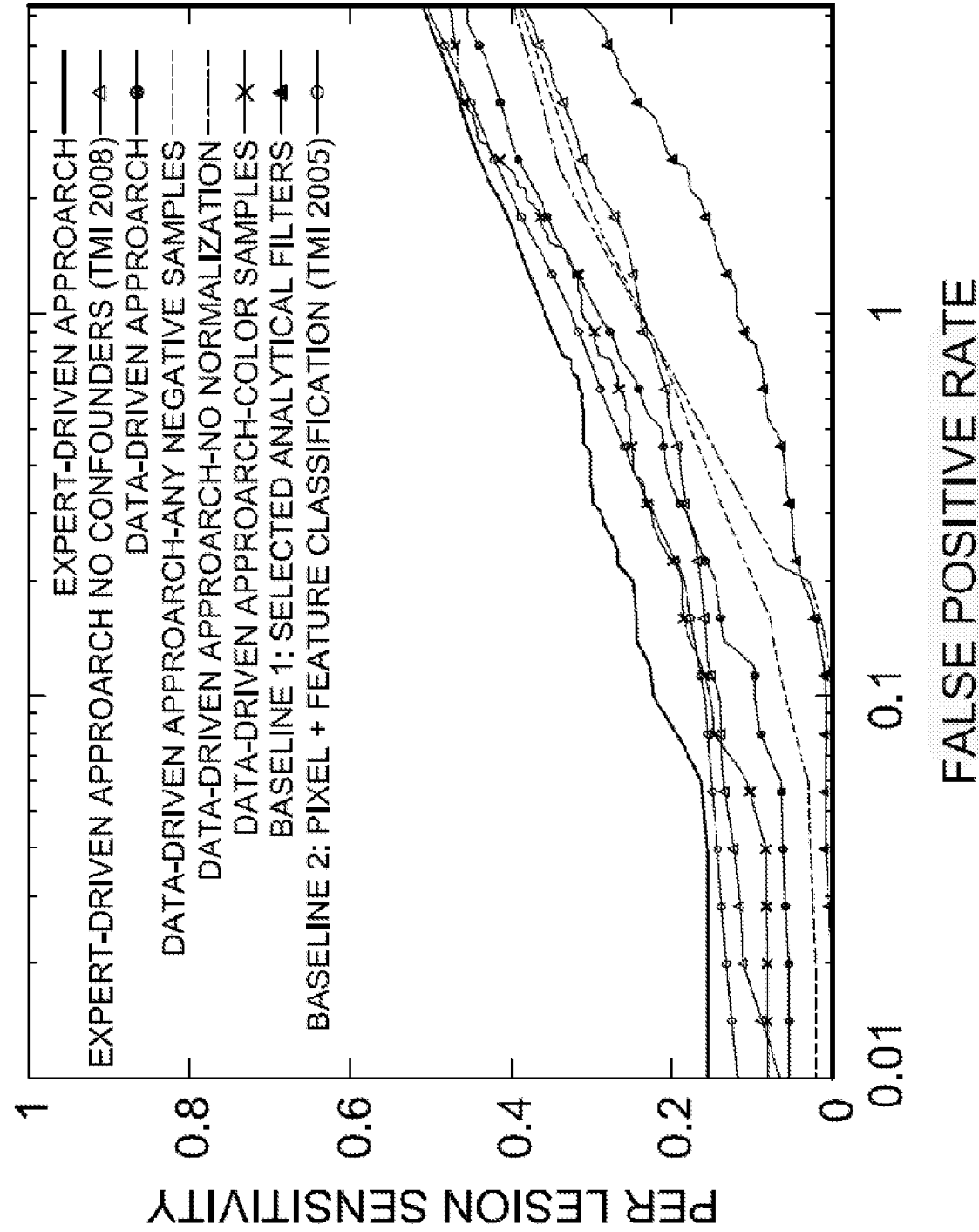


FIG. 9

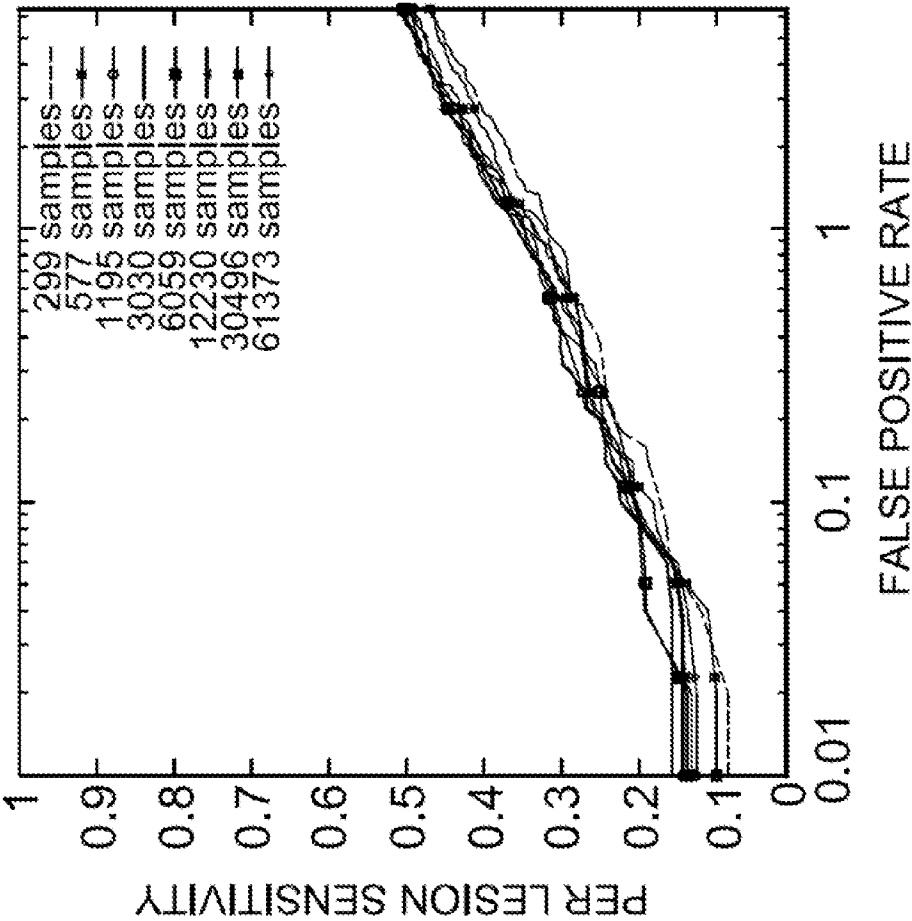


FIG. 10B

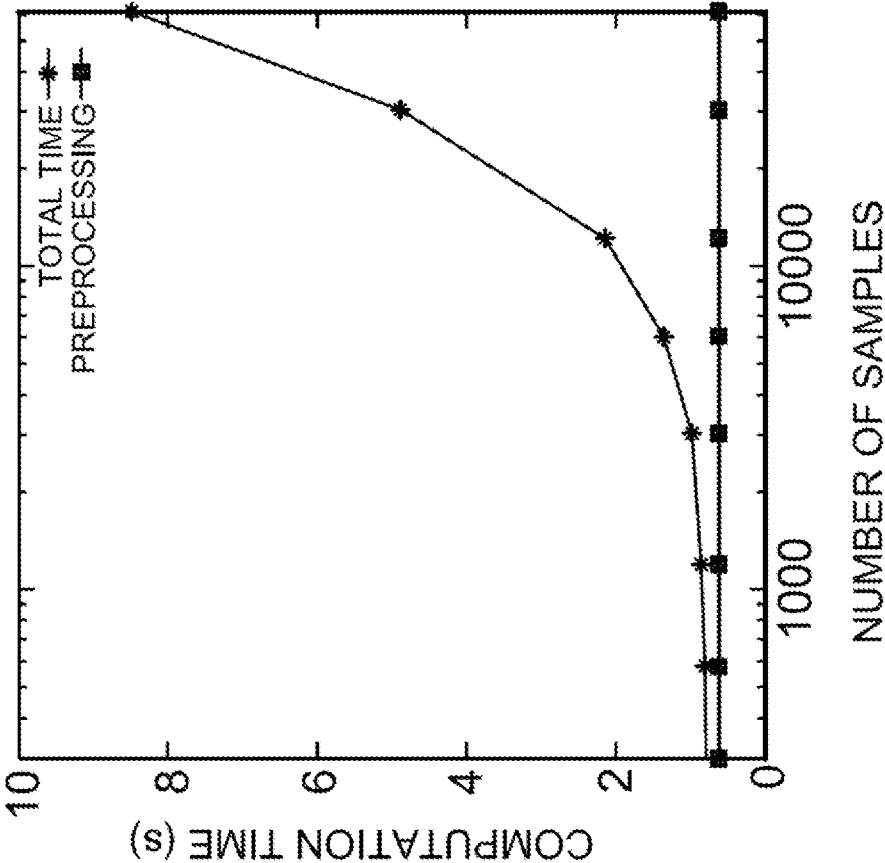


FIG. 10A

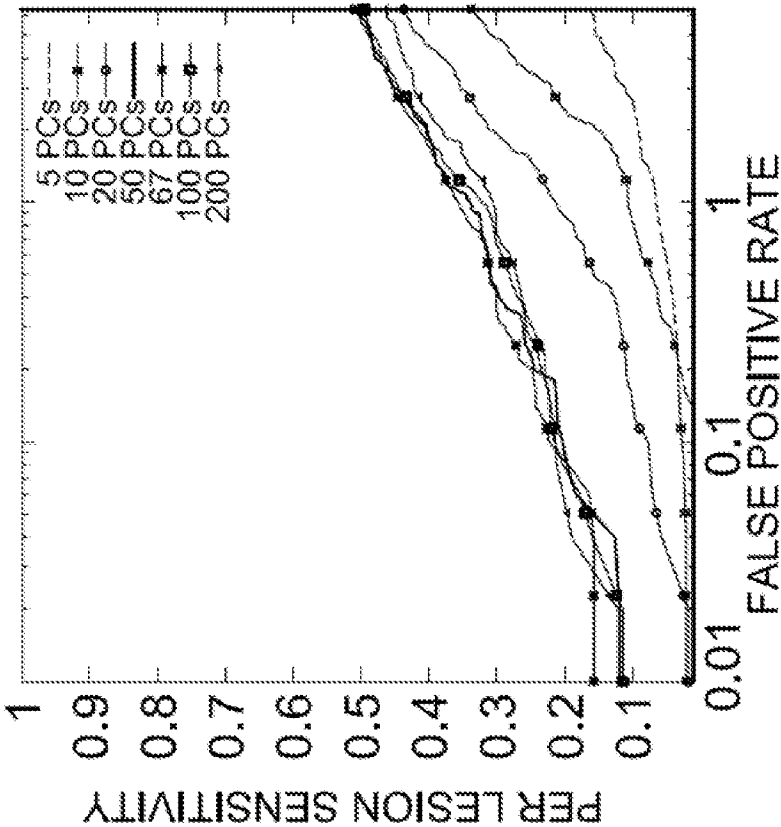


FIG. 10D

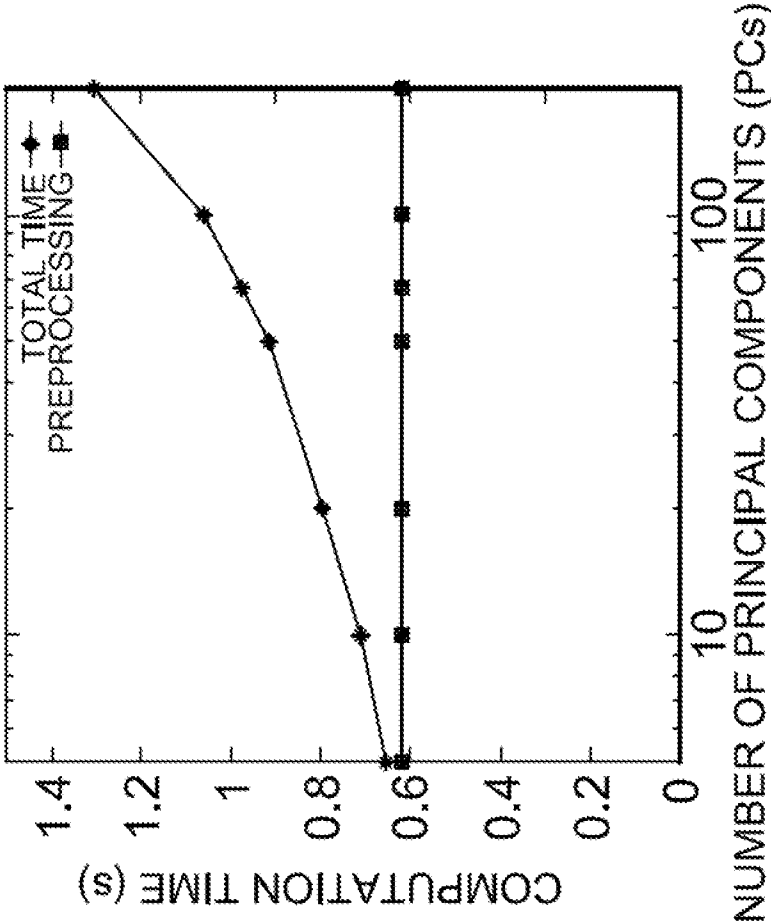


FIG. 10C

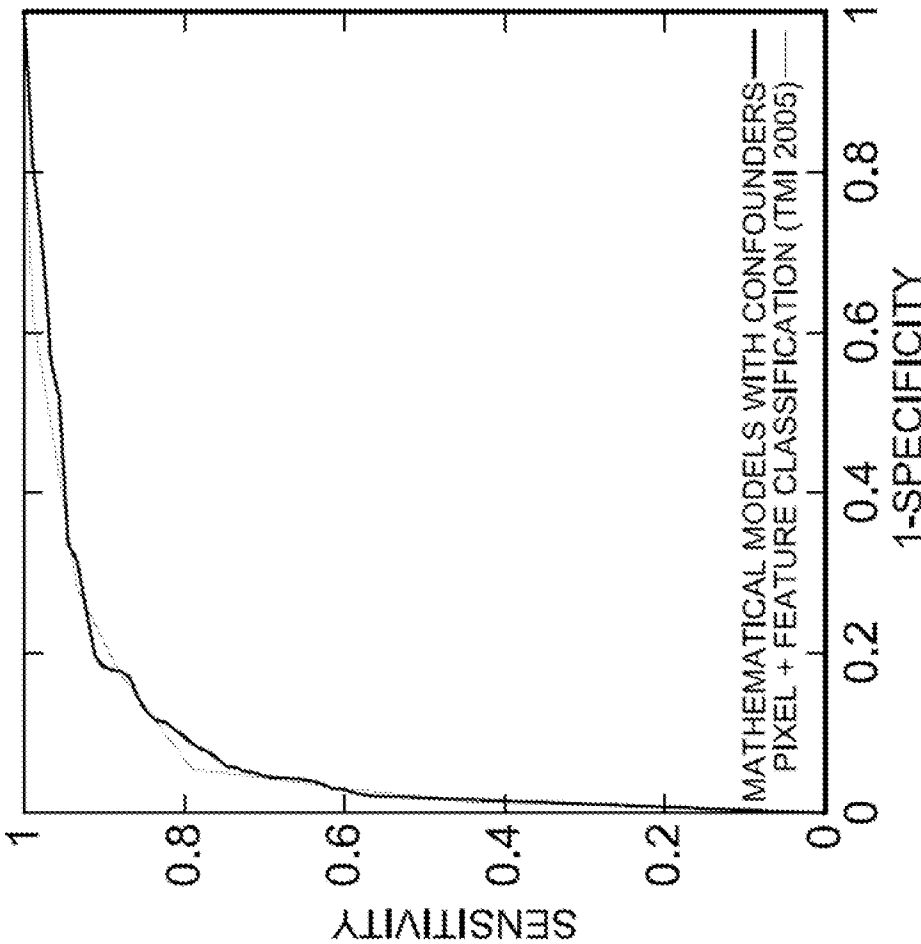


FIG. 11

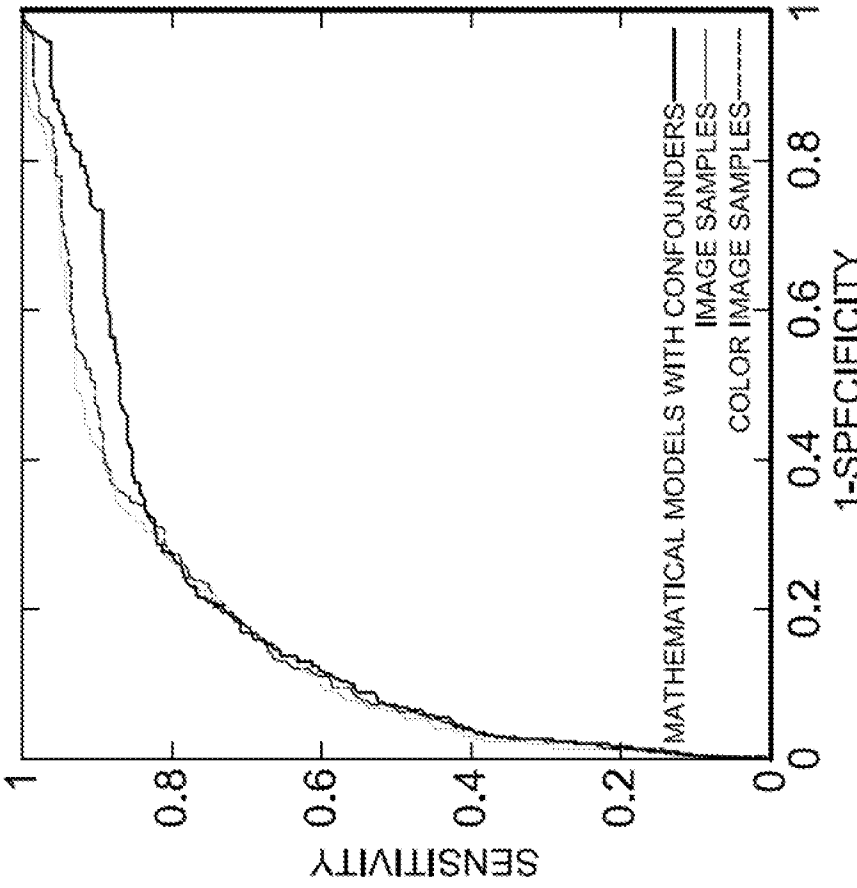
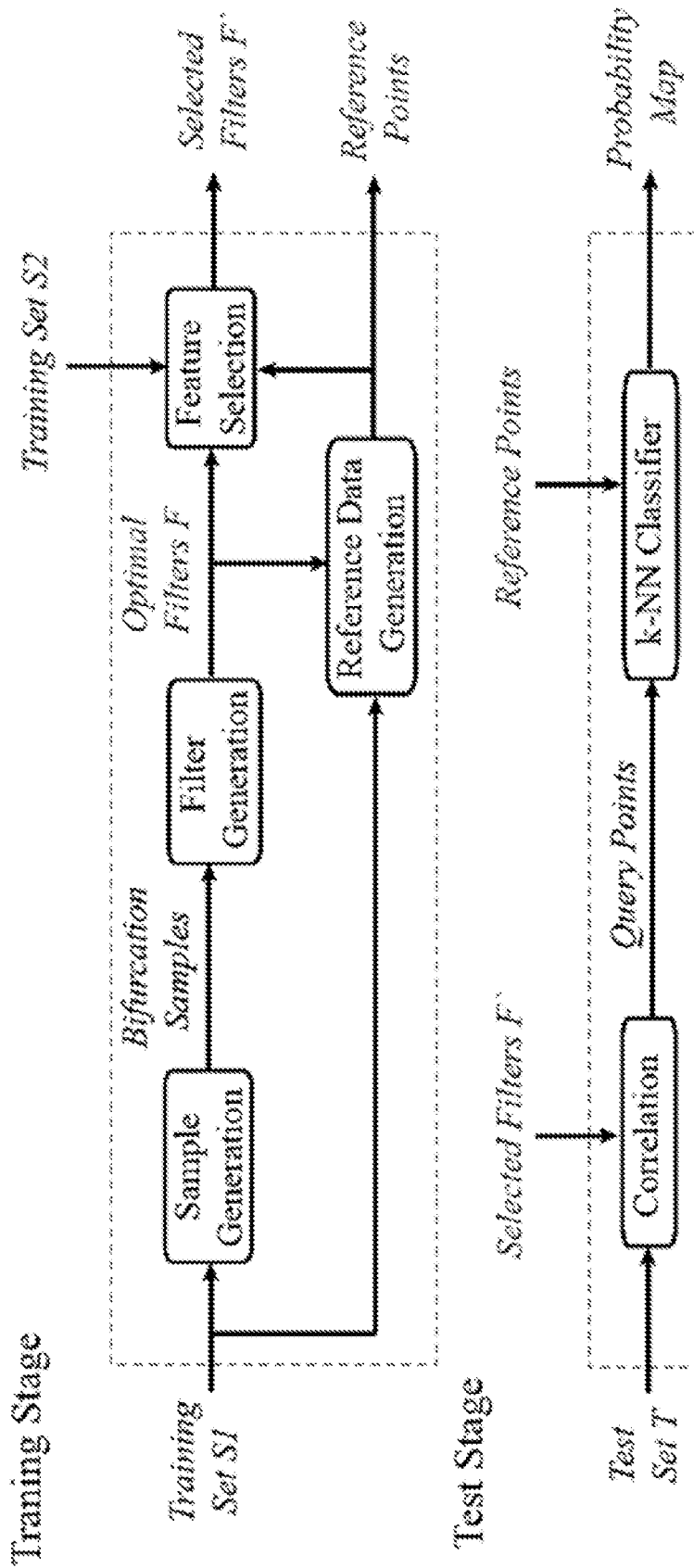


FIG. 12

FIG. 13A



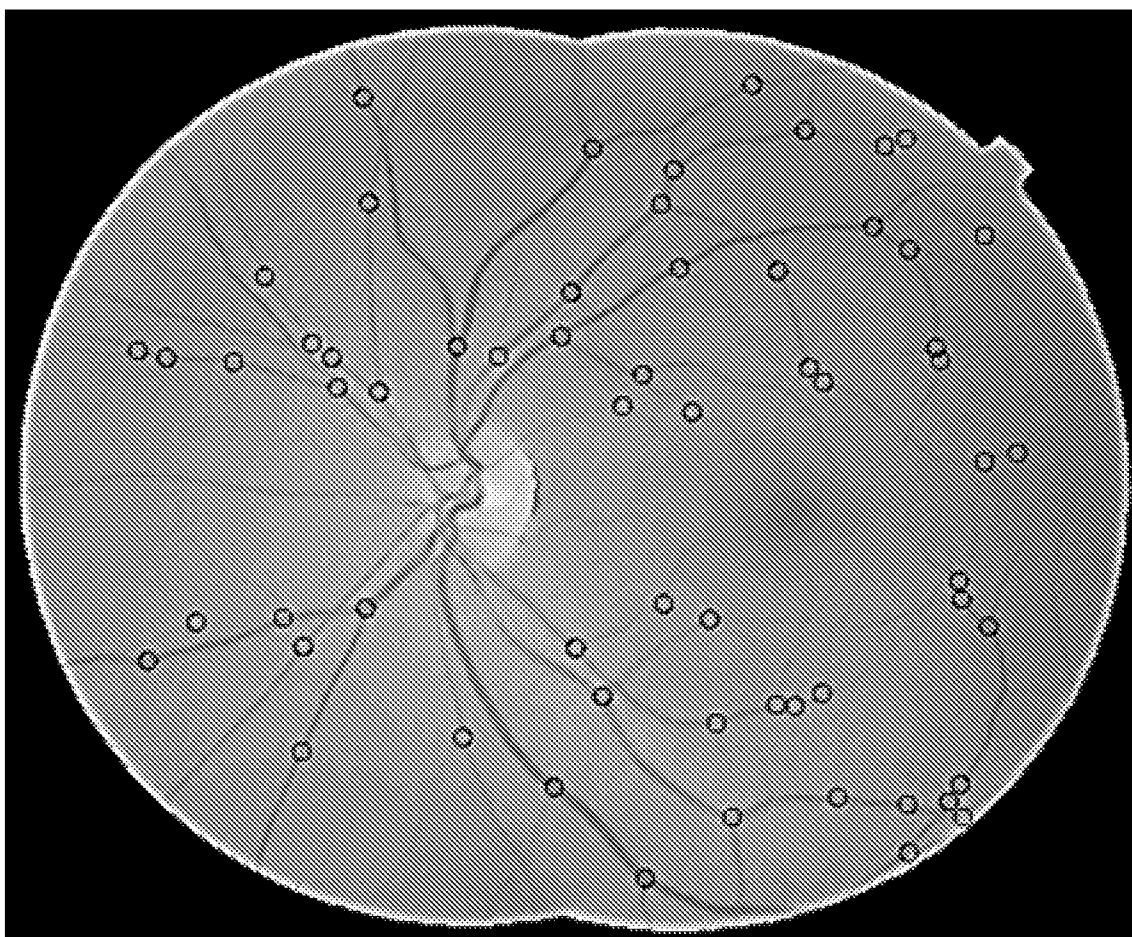


FIG. 13B

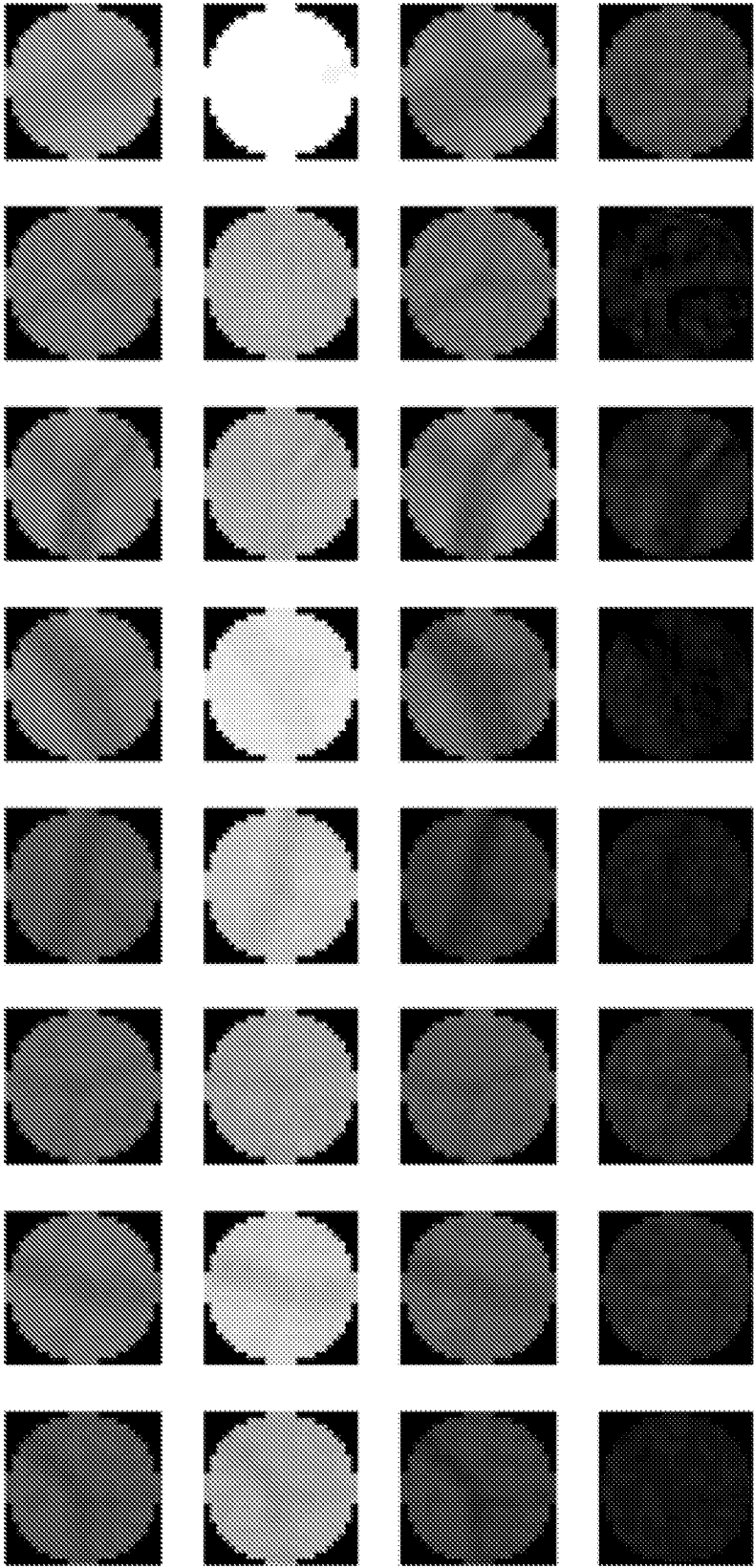


FIG. 13C

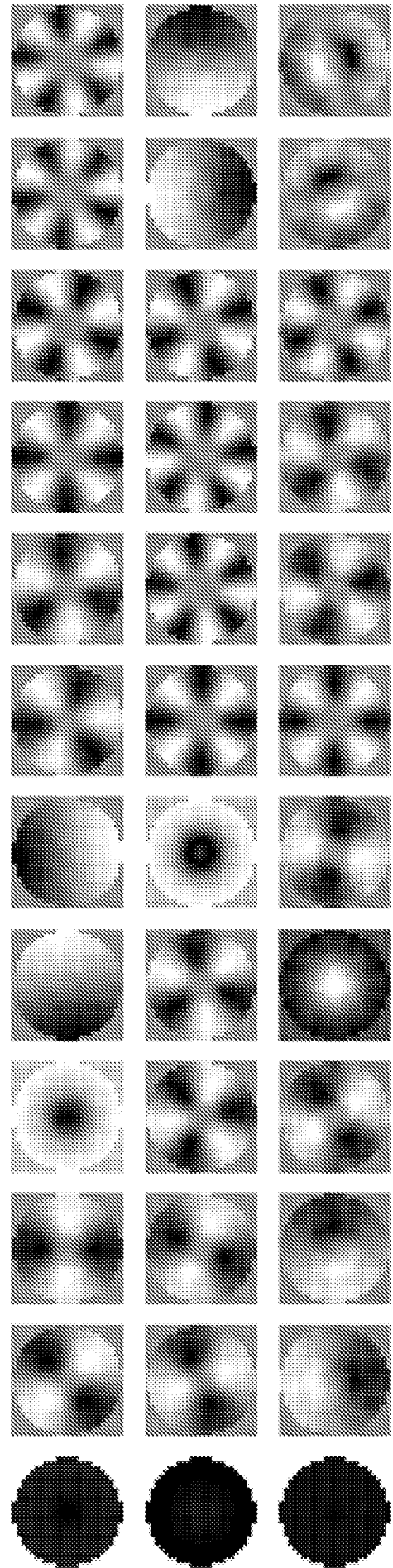


FIG. 14

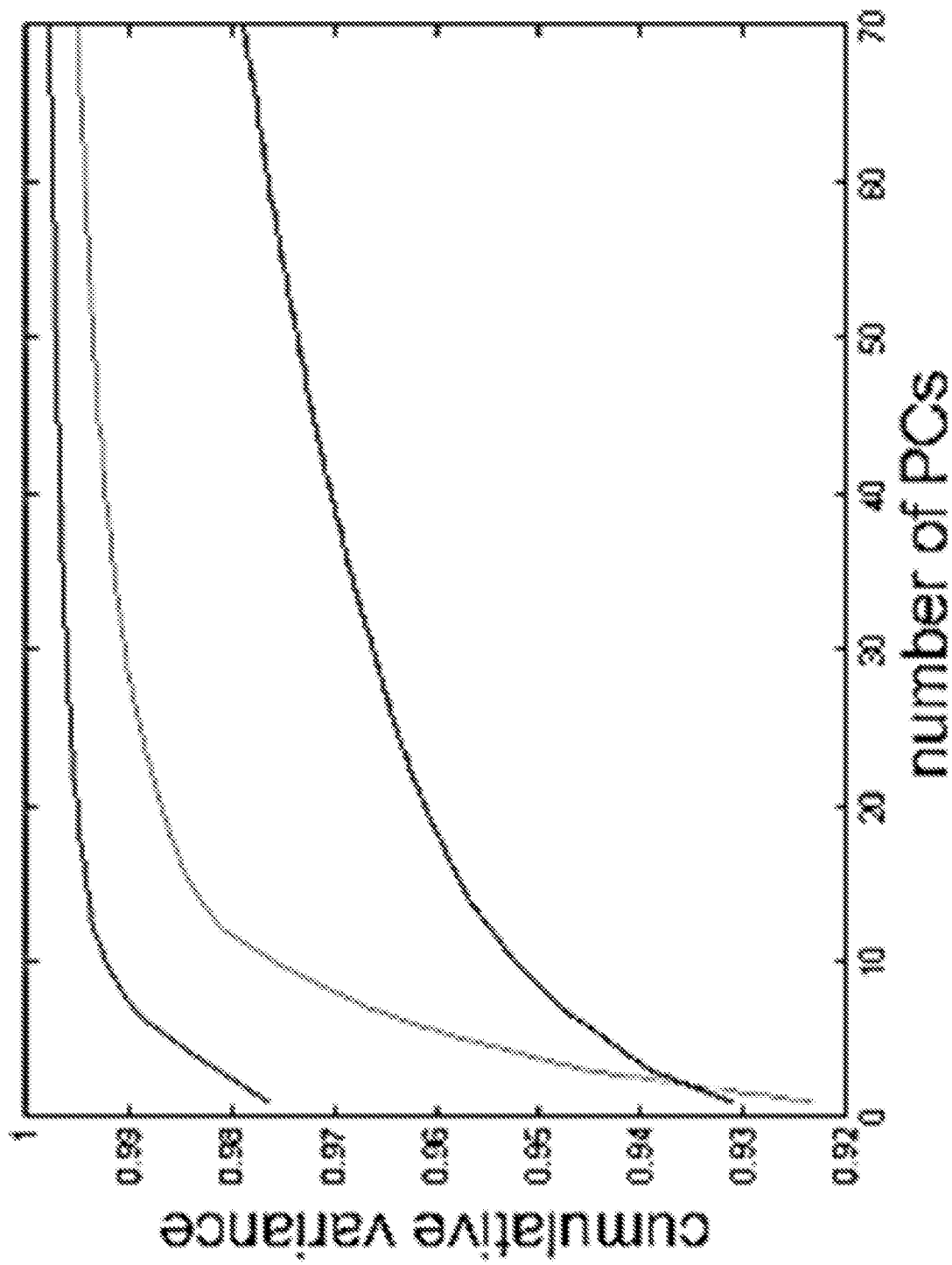


FIG. 15

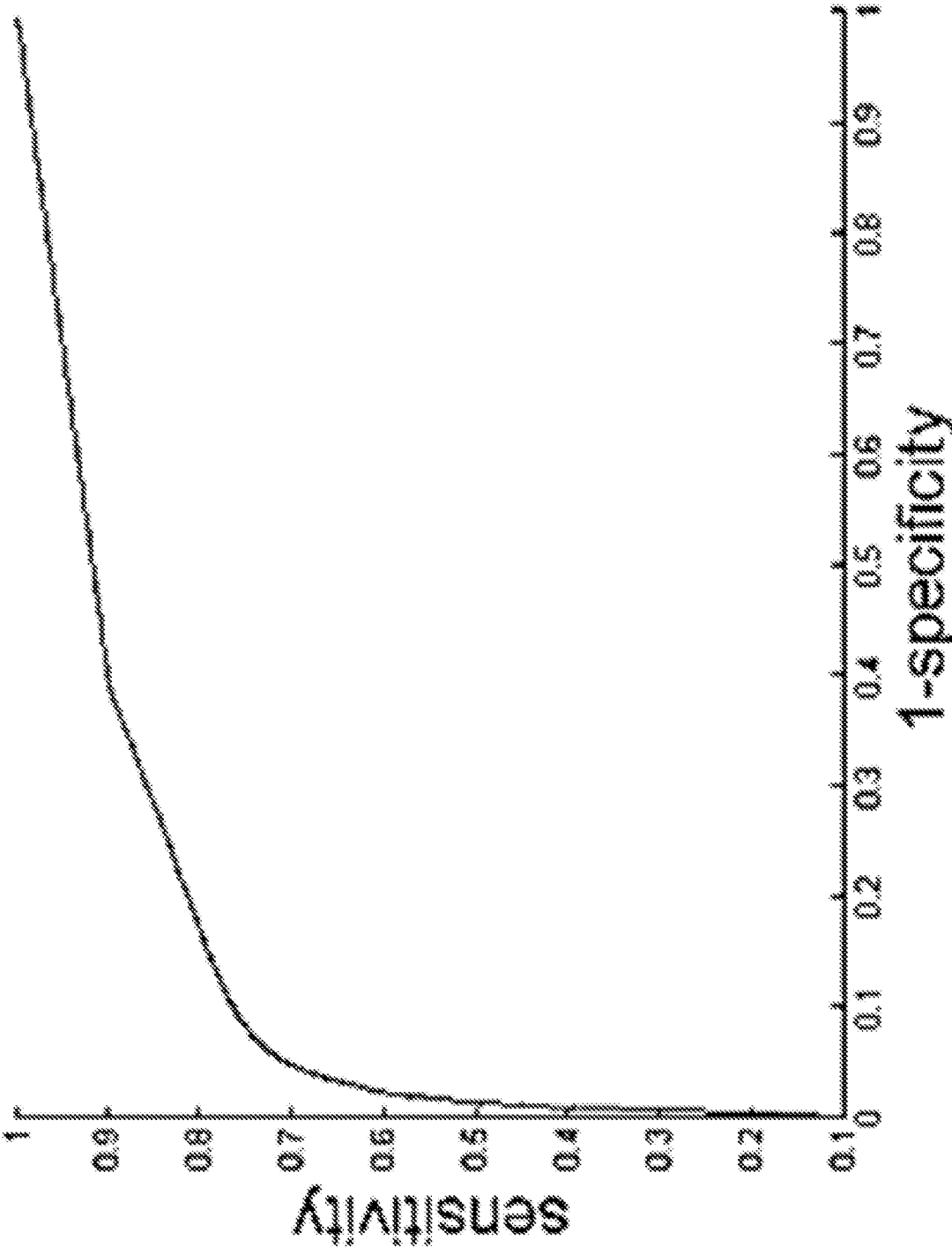


FIG. 16A

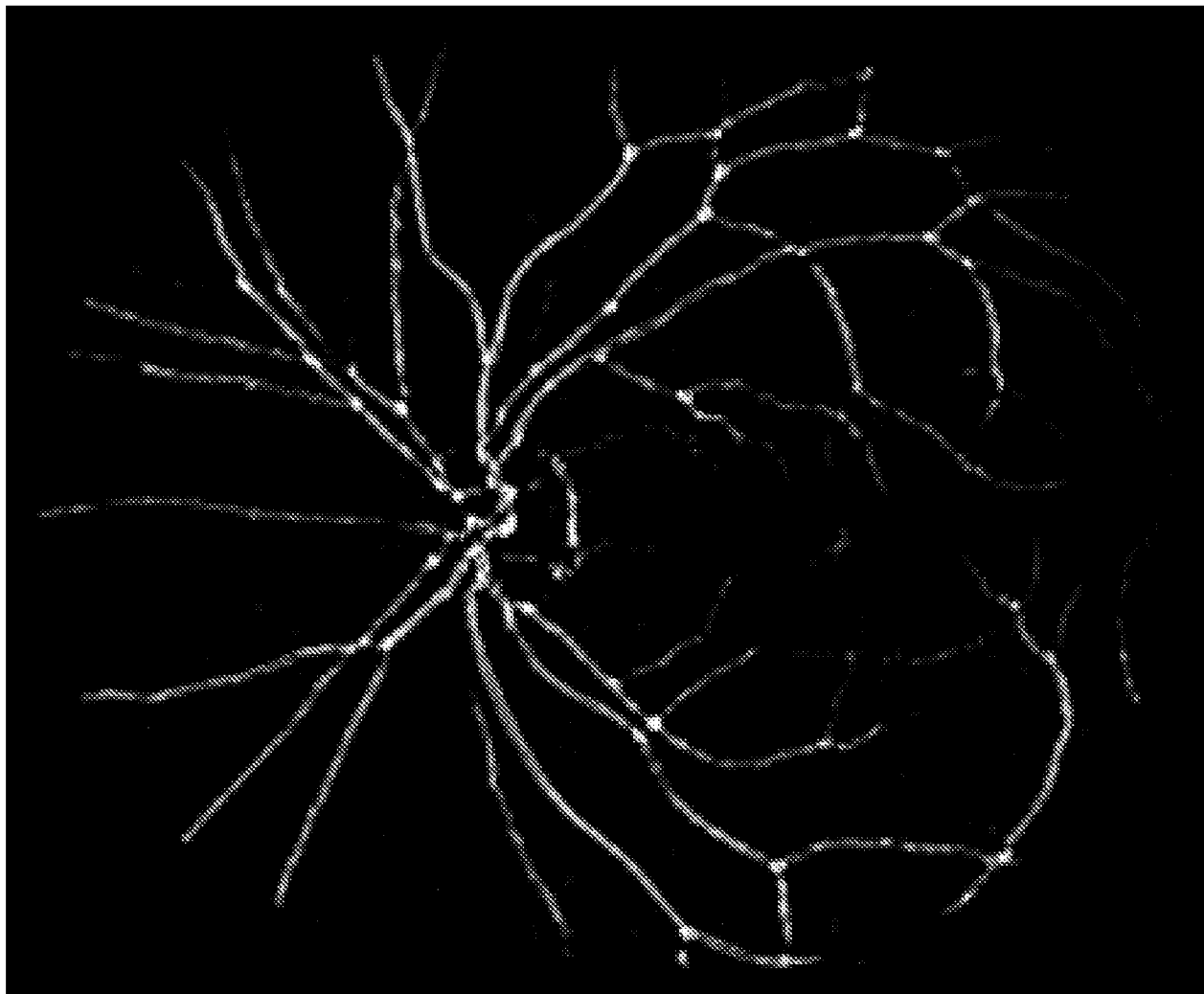


FIG. 16B

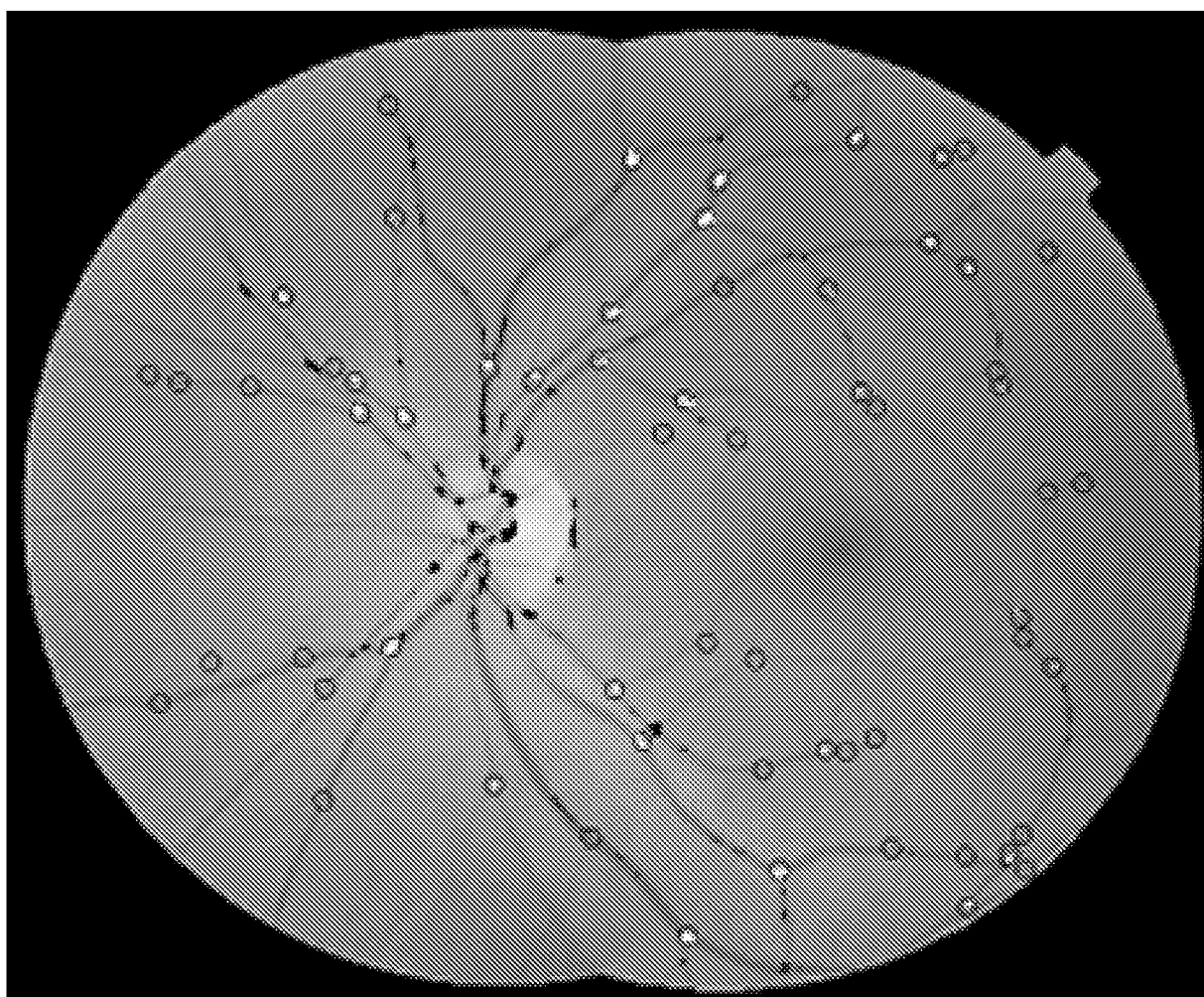


FIG. 16C

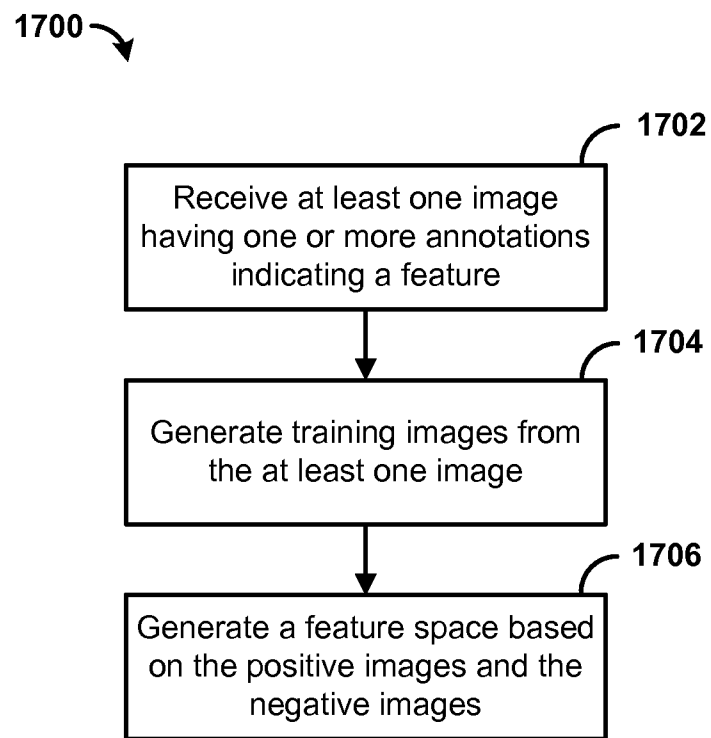


FIG. 17

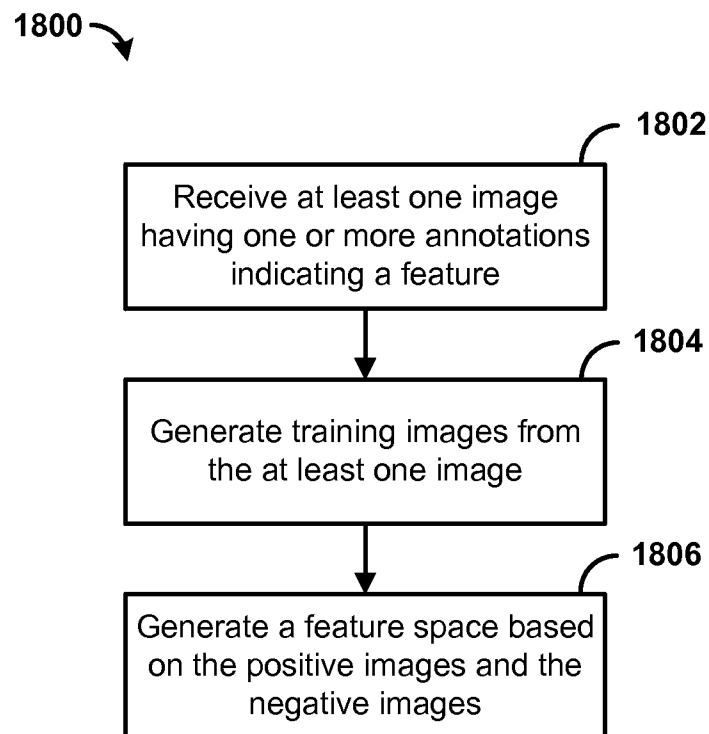


FIG. 18

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/14298

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - G06K 9/00 (2014.01) USPC - 382/128 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8): G06K 9/00 (2014.01) USPC: 382/128 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 382/128 or 382/131 or 382/134 IPC(8): G06K 9/00 (2014.01); CPC: G06T 7/0012 or G06F 19/321 or G06T 7/0083 or G06T 2207/30004 or G06T 7/0081 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Patbase; Google (Scholar, Patents); blood vessel, bifurcation, positive, negative, training, image, feature, feature space, annotation		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/078636 A1 (Abramoff et al.) 14 June 2012 (14.06.2012) entire document (especially para [0008], [0066]-[0070], [0082]-[0086], [00117]-[00124])	1-21
A	US 2009/0148024 A1 (Park) 11 June 2009 (11.06.2009) entire document	1-21
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 03 August 2014 (03.08.2014)		Date of mailing of the international search report 04 SEP 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774