(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2014 (12.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/138555 A1

(51) International Patent Classification:
G06K 9/40 (2006.01)

(21) International Application Number:
PCT/US2014/021659

(22) International Filing Date:
7 March 2014 (07.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/774,154 7 March 2013 (07.03.2013) US

(72) Inventor; and
(71) Applicant : **STURM, Bernhard** [DE/US]; 2245 Muir Woods Place, Davis, CA 95616 (US).

(74) Agents: **MEYERS, Thomas, C.** et al.; Brown Rudnick LLP, One Financial Center, Boston, MA 02111 (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))*

(54) Title: MULTIMODAL SEGMENTATION IN INTRAVASCULAR IMAGES

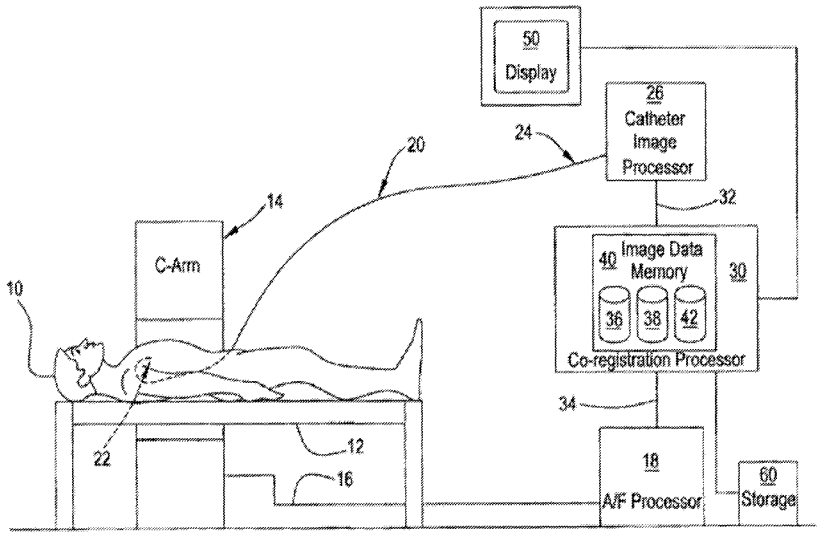


FIG. 1

(57) Abstract: The invention provides methods for detecting features of interest in cardiovascular images by receiving information from a first modality and transforming information from the first modality into a first coordinate space, receiving information from a second modality and transforming information from the second modality into a second coordinate space. The first coordinate space is aligned to the second coordinate space to combine information from the first modality and the second modality into a combined data set. The method can also involve detecting the feature of interest in a vascular image based on the combined data set.

WO 2014/138555 A1

MULTIMODAL SEGMENTATION IN INTRAVASCULAR IMAGES

Cross-Reference to Related Application

This application claims the benefit of, and priority to, U.S. Provisional Patent Application Serial No. 61/774,154, filed March 7, 2013, the contents of which are incorporated by reference.

Field of the Invention

The present invention generally relates to detecting features of interest in vascular images.

Background

Cardiovascular disease frequently arises from the accumulation of atheromatous deposits on inner walls of vascular lumen, particularly the arterial lumen of the coronary and other vasculature, resulting in a condition known as atherosclerosis. These deposits can have widely varying properties, with some deposits being relatively soft and others being fibrous and/or calcified. In the latter case, the deposits are frequently referred to as plaque. These deposits can restrict blood flow, leading to myocardial infarction in more severe cases.

The assessment and subsequent treatment of cardiovascular disease often utilizes various imaging modalities to image the interior of the vasculature. These imaging modalities can include fluoroscopic imaging, optical coherence tomography (OCT) imaging, intravascular ultrasound (IVUS) imaging, and virtual histology intravascular (VH-IVUS) imaging, among others. Fluoroscopy uses x-rays to obtain real-time moving images of a structure or object. OCT uses reflected light to create depth-resolved images. IVUS utilizes ultrasonic echoes to acquire images of the blood vessel and surrounding area. VH-IVUS is an imaging technique that produces a color-coded map of the arterial vessel, wherein different histological constituents are assigned different colors.

While all these modalities are useful in their own way, they also have their limits, particularly when detecting certain features of interest. For example, conventional grayscale IVUS cannot be used to image a stent placed inside the vessel without considerable difficulty. In

addition, conventional IVUS also cannot easily image luminal borders due to the presence of blood in the vessel. The limitations of these imaging modalities can hinder efforts to properly diagnose and treat cardiovascular disease.

Summary

The present invention provides methods for detecting features of interest in vascular images based on co-registered sets of data derived from multiple imaging modalities. Unlike conventional imaging techniques that rely on only one imaging modality to detect a feature of interest, the invention uses potentially complimentary information from multiple imaging modalities and combines the extracted information to facilitate detecting a feature of interest. The invention then uses the co-registered set of imaging data for analysis purposes. For instance, the feature of interest may be a cardiovascular stent, which is difficult to detect using conventional grayscale IVUS. In this example, the invention may involve obtaining an image of the area including and surrounding the stent using conventional grayscale IVUS. Information is then extracted from the image and transformed into positional data (i.e., a set of coordinates). The same area is then imaged with a second imaging modality, such as VH-IVUS. While stents in grayscale IVUS are difficult to detect, stents in VH-IVUS have a distinct appearance that is easily identifiable. By virtue of VH analysis, VH-IVUS and grayscale IVUS data sets are spatially co-registered, thereby providing a combined set of co-registered positional data. The features extracted from VH-IVUS can be combined with features extracted from the grayscale IVUS data to then train a search algorithm that can be used to identify stents back in conventional grayscale IVUS. A primary benefit of this multimodal detection approach is to take advantage of additional information obtained from complementary imaging modalities. This additional information may improve or facilitate the detection of features of interest in vascular sets.

Any imaging modality is useful for practicing the invention, including grayscale IVUS, VH-IVUS, OCT, MRI, X-ray angiography, and photoacoustic imaging. Moreover, the invention can be applied to facilitate the detection of any feature of interest using the aforementioned imaging modalities. Features of interest may be biological, such as the border or wall of a blood vessel. Features of interest may also be non-biological. Non-biological features of interest may

include medical devices that have been inserted into a bodily lumen, such as a stent, a balloon, or a catheter.

The invention also encompasses systems for practicing the above methods. Certain aspects of the invention are particularly amenable for computer implementation, such as the receipt and transformation of information from various imaging modalities, and the alignment of positional data from the multiple modalities into a combined data set. Accordingly, systems of the invention may include computers and processors for executing methods of the invention.

Brief Description of the Drawings

FIG. 1 shows a system for implementing intravascular image co-registration.

FIG. 2 depicts an illustrative angiogram image.

FIG. 3 depicts a fluoroscopic image of a radiopaque marker mounted upon a catheter.

FIG. 4 depicts an illustrative enhanced radiological image alongside a cross-sectional IVUS image.

FIG. 5 illustrates a system for practicing methods of the invention, according to certain embodiments.

FIG. 6 depicts an exemplary method for identifying a feature of interest.

FIG. 7 depicts an exemplary method for training a search algorithm for use in practicing methods of the invention.

FIG. 8 illustrates feature-based segmentation from a single image data set according to certain embodiments.

FIG. 9 illustrates feature-based segmentation from multiple/multimodal image data sets according to certain embodiments.

Detailed Description

The present invention provides methods for detecting features of interest in vascular images based on co-registered sets of data derived from multiple imaging modalities. The invention leverages potentially complimentary information from multiple imaging modalities and combines the information extracted from modality to facilitate detecting a desired feature of interest. In certain aspects, the invention may involve receiving information from a first imaging modality and transforming information from the first modality into a first coordinate space, i.e.,

positional data or a set of coordinates. The invention may also involve receiving information from a second imaging modality and transforming information from the second modality into a second coordinate space. The invention may further involve aligning the first coordinate space and the second coordinate space, thereby combining information from the first modality and the second modality into a combined data set. The invention then applies information from the combined data set to search for a feature of interest in a selected modality. For example, the information may be used to train a search algorithm for detecting the feature of interest. Generally speaking, the invention utilizes information derived from co-registered data sets to facilitate detecting features of interest.

The alignment of positional data from multiple imaging modalities is typically referred to as co-registration. Co-registration generally refers to any method of re-aligning images, and in particular aligning or overlaying images from different modalities. Co-registration is often used to overlay structural and functional images as well as link functional scans to anatomical scans. The co-registration of images and positional data from multiple imaging modalities is known in the art. Details regarding image co-registration can be found in, for example, in U.S. Patent Nos. 8,298,147 and 8,620,055; and U.S. Pub. 2012/0155734, each of which are incorporated herein by reference.

An exemplary method of co-registration is now described which uses x-ray fluoroscopy and intravascular ultrasound to obtain a co-registered intravascular data set. The invention, however, encompasses any and all imaging modalities, including without limitation, intravascular ultrasound (IVUS), optical coherence tomography (OCT), x-ray angiography, Computerized Tomography (CT) angiography, and Magnetic Resonance (MR) angiography.

FIG. 1 shows a system of the invention useful for the co-registration of angiogram or fluoroscopy and intravascular ultrasound images. The radiological and ultrasound image data acquisition sub-systems are generally well known in the art. With regard to the radiological image data, a patient 10 is positioned upon an angiographic table 12. The angiographic table 12 is arranged to provide sufficient space for the positioning of an angiography/fluoroscopy unit c-arm 14 in an operative position in relation to the patient 10 on the table 12. Radiological image data acquired by the angiography/fluoroscopy c-arm 14 passes to an angiography/fluoroscopy processor 18 via transmission cable 16. The angiography/fluoroscopy processor 18 converts the received radiological image data received via the cable 16 into angiographic/fluoroscopic image

data. The angiographic/fluoroscopic ("radiological") image data is initially stored within the processor 18.

With regard to portions of the system associated with acquiring ultrasound image data, an imaging catheter 20, and in particular an IVUS catheter, is inserted within the patient 10 so that its distal end, including a diagnostic probe 22 (in particular an IVUS probe), is in the vicinity of a desired imaging location of a blood vessel. While not specifically identified in FIG. 1, a radiopaque material located near the probe 22 provides indicia of a current location of the probe 22 in a radiological image. By way of example, the diagnostic probe 22 generates ultrasound waves, receives ultrasound echoes representative of a region proximate the diagnostic probe 22, and converts the ultrasound echoes to corresponding electrical signals. The corresponding electrical signals are transmitted along the length of the imaging catheter 20 to a proximal connector 24. IVUS versions of the probe 22 come in a variety of configurations including single and multiple transducer element arrangements. In the case of multiple transducer element arrangements, an array of transducers is potentially arranged: linearly along a lengthwise axis of the imaging catheter 20, curvilinear about the lengthwise axis of the catheter 20, circumferentially around the lengthwise axis, etc.

The proximal connector 24 of the catheter 20 is communicatively coupled to a catheter image processor 26. The catheter image processor 26 converts the signals received via the proximal connector 24 into, for example, cross-sectional images of vessel segments. Additionally, the catheter image processor 26 generates longitudinal cross-sectional images corresponding to slices of a blood vessel taken along the blood vessel's length. The IVUS image data rendered by the catheter image processor 26 is initially stored within the processor 26.

The type of diagnostic imaging data acquired by the diagnostic probe 22 and processed by the catheter image processor 26 varies in accordance with alternative embodiments of the invention. In accordance with a particular alternative embodiment, the diagnostic probe 22 is equipped with one or more sensors (e.g., Doppler and/or pressure) for providing hemodynamic information (e.g., blood flow velocity and pressure)—also referred to as functional flow measurements. In such alternative embodiments functional flow measurements are processed by the catheter image processor 26. It is thus noted that the term "image" is intended to be broadly interpreted to encompass a variety of ways of representing vascular information including blood pressure, blood flow velocity/volume, blood vessel cross-sectional composition, shear stress

throughout the blood, shear stress at the blood/blood vessel wall interface, etc. In the case of acquiring hemodynamic data for particular portions of a blood vessel, effective diagnosis relies upon the ability to visualize a current location of the diagnostic probe 22 within a vasculature while simultaneously observing functional flow metrics indicative of cardiovascular disease. Co-registration of hemodynamic and radiological images facilitates precise treatment of diseased vessels. Alternatively, instead of catheter mounted sensors, the sensors can be mounted on a guidewire, for example a guidewire with a diameter of 0.018″ or less. Thus, in accordance with embodiments of the present invention, not only are a variety of probe types used, but also a variety of flexible elongate members to which such probes are mounted at a distal end (e.g., catheter, guidewire, etc.).

A co-registration processor 30 receives IVUS image data from the catheter image processor 26 via line 32 and radiological image data from the radiological image processor 18 via line 34. Alternatively, the communications between the sensors and the processors are carried out via wireless media. The co-registration processor 30 renders a co-registration image including both radiological and IVUS image frames derived from the received image data. In accordance with an embodiment of the present invention, indicia (e.g., a radiopaque marker artifact) are provided on the radiological images of a location corresponding to simultaneously displayed IVUS image data. The co-registration processor 30 initially buffers angiogram image data received via line 34 from the radiological image processor 18 in a first portion 36 of image data memory 40. Thereafter, during the course of a catheterization procedure IVUS and radiopaque marker image data received via lines 32 and 34 is stored within a second portion 38 and a third portion 42, respectively, of the image data memory 40. The individually rendered frames of stored image data are appropriately tagged (e.g., time stamp, sequence number, etc.) to correlate IVUS image frames and corresponding radiological (radiopaque marker) image data frames. In an embodiment wherein hemodynamic data is acquired rather than IVUS data, the hemodynamic data is stored within the second portion 38.

In addition, additional markers can be placed on the surface of the patient or within the vicinity of the patient within the field of view of the angiogram/fluoroscope imaging device. The locations of these markers are then used to position the radiopaque marker artifact upon the angiographic image in an accurate location.

The co-registration processor 30 renders a co-registration image from the data previously stored within the first portion 36, second portion 38 and third portion 42 of the image data memory 40. By way of example, a particular IVUS image frame/slice is selected from the second portion 38. The co-registration processor 30 identifies fluoroscopic image data within the third portion 42 corresponding to the selected IVUS image data from the second portion 38. Thereafter, the co-registration processor 30 superimposes the fluoroscopic image data from the third portion 42 upon the angiogram image frame retrieved from the first portion 36. Thereafter, the co-registered radiological and IVUS image frames are simultaneously displayed, along-side one another, upon a graphical display device 50. The co-registered image data frames driving the display device 50 are also stored upon a long-term storage device 60 for later review in a session separate from a procedure that acquired the radiological and IVUS image data stored in the image data memory 40.

While not shown in FIG. 1, a pullback device is incorporated that draws the catheter 20 from the patient at a controlled/measured manner. Such devices are well known in the art. Incorporation of such devices facilitates calculating a current position of the probe 22 within a field of view at points in time when fluoroscopy is not active.

FIG. 2 presents an angiographic “roadmap” image 200 in a desired projection (patient/vessel orientation) and magnification as captured by the angiography/fluoroscopy processor 18. By way of example, the image 200 is initially captured by an angiography procedure performed prior to tracking the IVUS catheter to the region of interest within a patient's vasculature. Performing the angiography procedure without the catheter 20 in the vessel provides maximal contrast flow, better vessel filling and therefore a better overall angiogram image. Thus, side branches such as side branch 210 and other vasculature landmarks can be displayed and seen clearly on the radiological image portion of a co-registered image displayed upon the graphical display device 50.

FIG. 3 shows catheter radiopaque marker 300 visible in a fluoroscopic image. Catheter 20 is tracked to its starting position (e.g., a position where an IVUS pullback procedure begins). Typically the catheter 20 is tracked over a previously advanced guidewire (not shown). Thereafter, a fluoroscopic image is obtained. In the image as shown in FIG. 3, the catheter radiopaque marker 300 is visualized, but the vessel lumen is not, due to the absence of contrast flow. However, a set of locating markers present in both the angiogram and fluoroscopy images

enable proper positioning (superimposing) of the marker image within the previously obtained angiogram image. Other ways of properly positioning the radiopaque marker image within the field of view of the angiogram image will be known to those skilled in the art in view of the teachings herein. Furthermore, the marker artifact can be automatically adjusted (both size and position) on the superimposed image frames to correspond to the approximate position of the transducers.

FIG. 4 presents an exemplary co-registration image that results from overlaying or superimposing the radiopaque marker artifact upon the angiogram image. The exemplary co-registration display 401 (including the correlated radiological and IVUS images) depicts a selected cross-sectional IVUS image 400 of a vessel. A radiological image 410 is simultaneously displayed along-side the IVUS image 400 on the display 50. The radiological image 410 includes a marker artifact 420, generated from radiological image data rendered by a fluoroscope image frame, superimposed on an angiogram background rendered from the first portion 36 of the memory 40. The fluoroscope image frame corresponds to the current location of the diagnostic probe 22 within a vessel under observation. Precise matching of the field of view represented in both the angiogram and fluoroscope images (i.e., precise projection and magnification of the two images) allows identification of the current position of the IVUS probe corresponding to the displayed IVUS image 400 in the right pane of the co-registered images displayed in FIG. 4. Discussion of image co-registration may be found in U.S. Patent No. 7,930,014, incorporated herein by reference.

Once the co-registered set of data is obtained, for example, by using the methods described above, the co-registered set of data can then be applied to facilitate detecting a feature of interest in a given modality. In certain embodiments, this may comprise using the co-registered data set to train a search algorithm for detecting the feature of interest in a given modality. For example, the feature of interest may be a stent. The stent and surrounding vasculature may be imaged with two imaging modalities, such as IVUS and VH-IVUS. Features are extracted from both and aligned to obtain a co-registered data set. This combined data set can then be used to train a search algorithm for detecting the stent in conventional grayscale IVUS, for example, where the detection of stents is often problematic. Suitable methods for training the search algorithm will now be described.

In certain aspects, a feature of interest is identified in an imaging modality through use of a search algorithm that has been trained on a co-registered intravascular data set. As described above, the co-registered intravascular data set comprises information regarding a feature of interest, such as a vessel wall, from a plurality of imaging modalities. Based on the information provided in the combined data set, the search algorithm is able to identify the feature of interest in a given imaging modality. The algorithm addresses certain factors or parameters in order to make a comprehensive evaluation and identify the feature of interest based on positional and other data accumulated from multiple imaging modalities. Generally speaking, the process involves obtaining an image with a first imaging modality, extracting the feature of interest from the image, and transforming the feature into positional data (i.e., a set of coordinates). The process further involves obtaining at least a second image of the area with a second imaging modality, extracting the feature of interest, and again transforming the feature into positional data. The positional data from the first and second imaging modalities are then combined into one data set via co-registration, and the combined data set is used to train a search algorithm configured to detect the feature of interest in a given imaging modality.

Training of the algorithm may comprise a series of iterative steps, with each successive step evaluating each new data (i.e., provided from an additional imaging modality) in combination with all data submitted in the previous steps of the cycle (prior imaging modalities) and relevant information about the feature of interest until all test data (i.e., positional data) entered or submitted for analysis are evaluated comprehensively. Upon completion of the final step, the analysis function terminates, and the search result is formed upon completion of the analysis function. The present invention also contemplates the modification or update of positional data based upon new information received from imaging modalities, which is included as part of the algorithm, as such data becomes available and would serve to improve the accuracy of the search.

The search algorithm of the present invention may be embodied in any suitable application, such as a computer program or code that can facilitate its use. The algorithm or application embodying the application may be stored in the internal or external hard drive of a computer, a portable drive or disc, a server, a temporary or permanent memory device, or any other storage means that can facilitate the use of the algorithm and/or the results derived from its use. The algorithm or application is preferably in communication with at least one processing

device that facilitates the predictive analysis, for example, a computer or network processor. The algorithm or associated application may be accessed locally (e.g., on a single or networked computer) or remotely (e.g., web-based network via the internet, or via the intranet).

This access to the algorithm or application may be facilitated via the use of any suitable equipment, including without limitation, a computer, an internet appliance, telephonic device, a wireless device, and the like. Access to the algorithm, the application embodying the algorithm or the results obtained from use of the algorithm may be secured or limited from general access or use via a password, encryption, biometric- or voice-activation, or other suitable means of protection.

As contemplated by the invention, the functions and embodiments described above can be implemented using software, hardware, firmware, hardwiring, or any combinations of these. Features implementing functions can also be physically located at various positions, including being distributed such that portions of functions are implemented at different physical locations.

As one skilled in the art would recognize as necessary or best-suited for performance of the methods of the invention, a computer system or machines of the invention include one or more processors (e.g., a central processing unit (CPU) a graphics processing unit (GPU) or both), a main memory and a static memory, which communicate with each other via a bus. Systems of the invention may include a computer and a processor as well as computer readable storage medium instructions that when executed, cause the computer to receive information from a first imaging modality and transform the information into a first coordinate space, receive information from a second imaging modality and transform the information into a second coordinate space, and align the first coordinate space with the second coordinate space, thereby combining information from the first modality and the second modality into a combined data set. The instructions may further cause the computer to detect a feature of interest in a third imaging modality based on the combine data set.

FIG. 5 diagrams a system 100 according to embodiments of the invention. System 100 preferably includes computer 249 (e.g., laptop, desktop, tablet, or smartphone). The computer 249 may be configured to communicate across a network 109. Computer 249 includes one or more processor 159 and memory 163 as well as an input/output mechanism 154. Where methods of the invention employ a client/server architecture, steps of methods of the invention may be performed using server 113, which includes one or more of processor 121 and memory 129,

capable of obtaining data, instructions, etc., or providing results via interface module 125 or providing results as a file 117. Server 113 may be engaged over network 109 through computer 249 or terminal 267, or server 113 may be directly connected to terminal 167, including one or more processor 175 and memory 179, as well as input/output mechanism 171.

System 100 or machines according to the invention may further include, for any of I/O 154 or 171 a video display unit (e.g., a liquid crystal display (LCD) or a cathode ray tube (CRT)). Computer systems or machines according to the invention can also include an alphanumeric input device (e.g., a keyboard), a cursor control device (e.g., a mouse), a disk drive unit, a signal generation device (e.g., a speaker), a touchscreen, an accelerometer, a microphone, a cellular radio frequency antenna, and a network interface device, which can be, for example, a network interface card (NIC), Wi-Fi card, or cellular modem.

Memory 163, 179, or 129 according to the invention can include a machine-readable medium on which is stored one or more sets of instructions (e.g., software) embodying any one or more of the methodologies or functions described herein. In a preferred embodiment, a computer system of the invention includes one or more memory device that is a tangible, non-transitory memory. The software may also reside, completely or at least partially, within the main memory and/or within the processor during execution thereof by the computer system, the main memory and the processor also constituting machine-readable media. The software may further be transmitted or received over a network via the network interface device.

FIG. 6 presents steps of methods of the invention. It will be understood that of the methods described herein, as well as any portion of the systems and methods disclosed herein, can be implemented by computer, including the devices described above. Preferably, each step is performed by a processor or connected medical imaging device. An image is obtained using a given modality in which a feature of interest requires identification 201. The modality, for example, may be grayscale IVUS, and the feature of interest is a stent, which is difficult to detect with grayscale IVUS. Information regarding a feature of interest is extracted from an imaging modality. The feature is the converted into a feature vector comprising positional data regarding the feature of interest. This data is then inputted into the central processing unit (CPU) of a computer 202. The CPU is coupled to a storage or memory for storing instructions for implementing methods of the present invention, such as the search algorithm. The instructions, when executed by the CPU, cause the CPU to identify a selected feature of interest in an imaging

modality. The CPU provides this determination by inputting data from the imaging modality into an algorithm trained on a co-registered set of data derived from a plurality of imaging modalities for positional data regarding the feature of interest is known 203. The co-registered set of data may be stored locally within the computer, such as within the computer memory. Alternatively, the co-registered data set may be stored in a location that is remote from the computer, such as a server. In this instance, the computer communicates across a network to access the co-registered data set. The CPU then identifies the feature of interest in the imaging modality based on the data entered into the algorithm 204.

After preparing the co-registered set of positional data derived from a plurality of imaging modalities, well-known techniques such as cross-correlation, Principal Components Analysis (PCA), factor rotation, Logistic Regression (LogReg), Linear Discriminant Analysis (LDA), Eigengene Linear Discriminant Analysis (ELDA), Support Vector Machines (SVM), Random Forest (RF), Recursive Partitioning Tree (RPART), related decision tree classification techniques, Shrunken Centroids (SC), StepAIC, Kth-Nearest Neighbor, Boosting, Decision Trees, Neural Networks, Bayesian Networks, Support Vector Machines, and Hidden Markov Models, Linear Regression or classification algorithms, Nonlinear Regression or classification algorithms, analysis of variants (ANOVA), hierarchical analysis or clustering algorithms; hierarchical algorithms using decision trees; kernel based machine algorithms such as kernel partial least squares algorithms, kernel matching pursuit algorithms, kernel Fisher's discriminate analysis algorithms, or kernel principal components analysis algorithms, or other mathematical and statistical methods can be used to develop the search algorithm. A co-registered set of positional data derived from a plurality of imaging modalities is used to train the algorithm. To identify a selected feature of interest in an imaging modality, positional data regarding the feature of interest is obtained from a plurality of imaging modalities, and combined into a co-registered set of positional data, which is then used as input data (inputs into a search algorithm fitted to the co-registered positional data obtained from the selected population of individuals). Any formula or algorithm may be used to combine positional data based on features of interest extracted from the various imaging modalities.

Although various preferred formula are described here, several other model and formula types beyond those mentioned herein and in the definitions above are well known to one skilled in the art. The actual model type or formula used may itself be selected from the field of

potential models based on the performance and diagnostic accuracy characteristics of its results in a training population. The specifics of the formula itself may commonly be derived from selected parameter results in the relevant training population. Amongst other uses, such formula may be intended to map the feature space derived from one or more selected parameter inputs to a set of subject classes, to derive an estimation of a probability function of risk using a Bayesian approach, or to estimate the class-conditional probabilities, then use Bayes' rule to produce the class probability function as in the previous case.

Preferred formulas include the broad class of statistical classification algorithms, and in particular the use of discriminant analysis. The goal of discriminant analysis is to predict class membership from a previously identified set of features. In the case of linear discriminant analysis (LDA), the linear combination of features is identified that maximizes the separation among groups by some criteria. Features can be identified for LDA using an eigengene based approach with different thresholds (ELDA) or a stepping algorithm based on a multivariate analysis of variance (MANOVA). Forward, backward, and stepwise algorithms can be performed that minimize the probability of no separation based on the Hotelling-Lawley statistic.

Eigengene-based Linear Discriminant Analysis (ELDA) is a feature selection technique developed and reported in Shen et al., 2006, Eigengene-based linear discriminant model for tumor classification using gene expression microarray data, Bioinformatics 22(21):2635-2642. The formula selects features (e.g. parameters) in a multivariate framework using a modified Eigen analysis to identify features associated with the most important eigenvectors. “Important” is defined as those eigenvectors that explain the most variance in the differences among samples that are trying to be classified relative to some threshold.

A support vector machine (SVM) is a classification formula that attempts to find a hyperplane that separates two classes. This hyperplane contains support vectors, data points that are exactly the margin distance away from the hyperplane. In the likely event that no separating hyperplane exists in the current dimensions of the data, the dimensionality is expanded greatly by projecting the data into larger dimensions by taking non-linear functions of the original variables (Venables and Ripley, 2002, Modern Applied Statistics with S 4Ed, Springer Verlag). Although not required, filtering of features for SVM often improves prediction. Features (e.g., parameters/biomarkers) can be identified for a support vector machine using a non-parametric Kruskal-Wallis (KW) test to select the best univariate features. A random forest or recursive

partitioning (RPART, Breiman et al., 1984) can also be used separately or in combination to identify parameter combinations that are most important. Random forests and recursive partitioning are discussed in Strobl et al., 2009, An Introduction to Recursive Partitioning: Rationale, Application and Characteristics of Classification and Regression Trees, Bagging and Random Forests, Psychol Methods 14(4):323–348; Breiman, 2001, Random forests, Machine Learning 45:5-32; Breiman, 1984, Classification and Regression Trees, Boca Raton: Chapman & Hall/CRC; U.S. Pat. 8,600,917; and U.S. Pat. 8,187,830, incorporated by reference. Both KW and RF require that a number of features be selected from the total. RPART creates a single classification tree using a subset of available parameters.

Other formula may be used in order to pre-process the results of individual selected parameter measurement into more valuable forms of information, prior to their presentation to the predictive formula. Most notably, normalization of parameter results, using either common mathematical transformations such as logarithmic or logistic functions, as normal or other distribution positions, in reference to a population's mean values, etc. are all well known to those skilled in the art.

In addition to the individual parameter values of one subject potentially being normalized, an overall predictive formula for all subjects, or any known class of subjects, may itself be recalibrated or otherwise adjusted based on adjustment for a population's expected prevalence and mean parameter values, according to the technique outlined in D 'Agostino et al., 2001, Validation of the Framingham coronary heart disease prediction score: results of a multiple ethnic group investigation, JAMA 286:180-187, or other similar normalization and recalibration techniques. Such adjustment statistics may be captured, confirmed, improved and updated continuously through a registry of past data presented to the model, which may be machine readable or otherwise, or occasionally through the retrospective query of stored samples or reference to historical studies of such parameters and statistics. Additional examples that may be the subject of formula recalibration or other adjustments include statistics used in studies by on the limitations of odds ratios (see Pepe et al., 2004, Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker, Am J Epidemiology 159(9):882-890) and receiver operating characteristic (ROC) curve in risk prediction (see Cook, 2007, Use and misuse of receiver operating characteristic curve in risk prediction, Circulation 115(7):928-35; Wang et al., 2006, Multiple biomarkers for the prediction of first major cardiovascular events

and death, NEJM 355:2631-2639; and Grund & Sabin, 2010, Analysis of biomarker data: logs, odds, ratios and ROC curves, Curr Opin HIV AIDS 5(6):473-479). In addition, , the numeric result of a classifier formula itself may be transformed post-processing by its reference to an actual positive controls in which the selected feature of interest has already been identified and confirmed.

FIG. 7 is a flow diagram representing an exemplary method for model development 300 which may be used to search for a feature of interest. The method 300 may be implemented using the example computing system environment 100 of FIG. 5 and will be used to explain the operation of the environment 100. However, it should be recognized that the method 300 could be implemented by a system different than the computing system environment 100. At a block 301, a co-registered set of positional data regarding a selected feature of interest, as has been described herein, is obtained from a data storage device, such as the system memory 129, an internal or external database, or other computer storage media. The co-registered data set may be initially derived through a variety of means, including various imaging modalities capturing the feature of interest in an image, in which the feature is extracted from the imaging modality and converted into positional data (i.e., a set of coordinates).

At a block 302, co-registered data set is prepared as needed to meet the requirements of the model or analysis that will be used to train the search algorithm, as described below. For example, data set preparation may include preparing the positional data from each imaging modality, or a chosen subset thereof. When necessary, various data preparation methods may be used to prepare the data prior to training the algorithm, such as gap fill techniques (e.g., nearest neighbor interpolation or other pattern recognition), quality checks, data combination using of various formulae (e.g., statistical classification algorithms), normalization and/or transformations, such as logarithmic functions to change the distribution of data to meet model requirements (e.g., base 10, natural log, etc.). Again, the particular data preparation procedures are dependent upon the model or models that will be trained using the co-registered data set. The particular data preparation techniques for various different model types are known, and need not be described further.

At a block 303, the particular extracted features are transformed into positional data used to select parameters that are subsequently used in the training of the search model used to identify the feature of interest in a given imaging modality. Use of the co-registered positional

data may involve utilizing only the positional data from the co-registered set that provides the most reproducible results. Examples of data set validation may include, but are not limited to, cross-validation and bootstrapping. From the parameter selection, the optimal search model for identifying a feature of interest in a given imaging modality may be determined and selected. However, it is noted that not all models provide the same results with the same data set. For example, different models may utilize different aspects of the positional data and produce different results, thereby adding significance to the selected positional data in the optimized model. Accordingly, multiple selection models may be chosen and utilized with the co-registered data set, or subsets of the co-registered data set, in order to identify the optimal search model for identifying a feature of interest in a given modality. Examples of the particular models, including statistical models, algorithms, etc., which may be used for selecting the positional data from the co-registered data sets have been described above.

For each selection model used with the data set, or subset thereof, the positional data is selected based on its statistical significance in the model. When inputted into each model, the positional data is selected based on various criteria for statistical significance, and may further involve cumulative voting and weighting. Tests for statistical significance may include exit-tests and analysis of variance (ANOVA). The model may include classification models (e.g., LDA, logistic regression, SVM, RF, tree models, etc.) and survival models (e.g., cox), many examples of which have been described above.

At a block 304, the search model to be used for identifying a feature of interest is selected, trained and validated. In particular, leading candidate models may be selected based on one or more performance criteria, examples of which have been described above. For example, from using the data set, or data subsets, with various models, not only are the models used to determine statistically significant parameters, but the results may be used to select the optimal models along with the parameters. As such, the evaluation model used to evaluate risk may include one of those used as a selection model, including classification models and survival models. Combinations of models markers, including marker subsets, may be compared and validated in subsets and individual data sets. The comparison and validation may be repeated many times to train and validate the model and to choose an appropriate model, which is then used as an evaluation model for evaluating risk of a diabetic condition.

Reference will now be made applications of the invention in specific scenarios. It is to be understood that these embodiments are not limiting. As illustrated in the following examples, the invention relates to the detection of features of interest, such as vessel borders and stent struts, in vascular images derived from multiple data sets or imaging modalities. Methods of the invention leverage potentially complimentary information from multiple imaging modalities and combine the information extracted from each image to detect the target feature.

Image segmentation is the process of partitioning a digital image into multiple segments (sets of pixels, also known as superpixels). The goal of segmentation is to simplify and/or change the representation of an image into something that is more meaningful and easier to analyze. Image segmentation is typically used to locate objects and boundaries (lines, curves, etc.) in images. One approach to segmentation is to compute and extract features from the image data. The features can be combined into a feature vector (e.g., transformed into positional data), that can then be matched to known feature vectors (i.e., gold standard information) or run through a trained classifier (e.g., a neural network or other algorithm) to classify the image data into predetermined classes.

FIG. 8 diagrams a process of partitioning a digital image into multiple segments. AS shown in FIG. 8, and image is obtained 801, and features are extracted 802 from the image. The features are then combined into a feature vector 803 (e.g., transformed into positional data) that can then be used to train a search algorithm 804 to identify the selected feature of interest in a given modality 805. Given a set of spatially co-registered intravascular images obtained from multiple imaging modalities, however, features can be computed and extracted from the multiple images and combined into a single feature vector. If the multimodal source a co-registered data set based on multiple imaging modalities is able to provide complementary information, the resulting feature vector contains more information than if extracted from a single source. Accordingly, the search algorithm trained on this co-registered set of data should provide more accurate results.

FIG. 9 illustrates images captured by multiple imaging modalities 901 and gives an example of the image segmentation process. As noted above, any imaging modality can be used in accordance with the invention. For example, the imaging modalities depicted in FIG. 9 could comprise IVUS, x-ray angiography, and OCT. After the image is obtained 901, the features are extracted from the images 902 and transformed into positional data 903. The positional data is

then combined and aligned into a co-registered set of data 904. This co-registered set of data 904 is then used to train a search algorithm 905 that can be used to identify a feature of interest in a given modality 906. Methods of the invention can be easily applied in the following, non-limiting, scenarios.

VH-IVUS (Virtual Histology-Intravascular Ultrasound) and grayscale IVUS (Intravascular Ultrasound): Stents are known to be difficult to detect using conventional grayscale IVUS. Methods of the invention, however, can be used to detect non-biological features of interest by combining the complementary imaging modalities of IVUS and VH-IVUS to provide more information. By virtue of VH analysis, VH-IVUS and grayscale IVUS data are already spatially co-registered. Stents in VH-IVUS have a distinct appearance which can be easily identified in IVUS images. This information can be used to initialize a search method for stent detection in the grayscale IVUS data set or combined with features extracted from the grayscale IVUS data set as part of a stent detection algorithm.

Grayscale IVUS and OCT stent detection: As noted above, stents are difficult to detect using grayscale IVUS alone. In this example, methods of the invention utilize a co-registered set of IVUS and OCT data to assist in stent detection. Given a set of spatially co-registered grayscale IVUS and OCT data sets, features can be extracted from each modality and combined into a single feature vector as described above. This example can be expanded to an approach encompassing VH-IVUS, grayscale IVUS, and OCT.

Grayscale IVUS and OCT vessel and lumen border detection: This example is the same as the above, however, the features of interest are now biological rather than non-biological. This particular combination of imaging modalities can be significantly advantageous as detection of lumen borders with grayscale IVUS alone can be extremely challenging due to the presence of blood. OCT, on the other hand, acquires image data in a flushed vessel, which facilitates imaging the lumen borders. If the feature of interest is a vessel border, then the OCT data becomes less significant, except for the fact that the vessel border is always outside the lumen and the OCT data is well-suited to identifying the lumen.

It is to be understood that these examples are not limiting, and that the invention includes all imaging modalities and all features of interest, whether they be biological or non-biological. For example, this vascular multimodal approach can also be applied to x-ray angiography and/or CT angiography data co-registered with IVUS and/or OCT data sets. Furthermore, the invention

is not limited to IVUS and OCT as the only intravascular imaging modalities. Other suitable intravascular imaging modalities include MRI and photoacoustic imaging. A primary benefit of the multimodal approach described herein is to take advantage of additional information derived from complementary imaging modalities when available. This additional information improves or facilitates the detection of features of interest in vascular data sets when used in accordance with the provided methods.

Incorporation by Reference

References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, have been made throughout this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes.

Equivalents

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

What is claimed is:

1.A method for detecting a feature of interest in a vascular image, the method comprising:

receiving information from a first imaging modality and transforming information from the first imaging modality into a first coordinate space;

receiving information from a second imaging modality and transforming information from the second imaging modality into a second coordinate space;

aligning the first coordinate space and the second coordinate space, thereby combining information from the first modality and the second modality into a combined data set; and

detecting a feature of interest in a vascular image based on the combined data set.

2.The method of claim 1, wherein the imaging modality of the first and second imaging modality is selected from a group consisting of: intravascular ultrasound (IVUS), virtual histology intravascular ultrasound (VH-IVUS), optical coherence tomography (OCT), x-ray angiography, and magnetic resonance imaging.

3.The method of claim 1, wherein the first modality is different from the second imaging modality.

4.The method of claim 1, wherein receiving information comprises receiving information regarding the feature of interest.

5.The method of claim 1, wherein the feature of interest comprises a biological feature of interest.

6.The method of claim 5, wherein the biological feature of interest is a vessel or lumen wall.

7.The method of claim 1, wherein the feature of interest comprises a non-biological feature of interest

8.The method of claim 7, wherein the non-biological feature of interest is a stent.

9.The method of claim 1, wherein detecting the feature of interest comprises initializing a search for the feature of interest based on the combined data set.

10.The method of claim 1, wherein detecting the feature of interest comprises training an algorithm to detect the feature of interest based on the combined data set.

11.A system for determining the degree of improvement after a therapeutic procedure, the system comprising:

a processor; and

a computer readable storage medium comprising instructions that when executed cause the system to:

receive information from a first imaging modality and transform information from the first imaging modality into a first coordinate space;

receive information from a second imaging modality and transform information from the second imaging modality into a second coordinate space;

align the first coordinate space and the second coordinate space, thereby combining information from the first modality and the second modality into a combined data set; and

detect a feature of interest in a vascular image based on the combined data set.

12.The system of claim 11, wherein the imaging modality of the first and second imaging modality is selected from a group consisting of: intravascular ultrasound (IVUS), virtual histology intravascular ultrasound (VH-IVUS), optical coherence tomography (OCT), x-ray angiography, and magnetic resonance imaging.

13.The system of claim 11, wherein the first modality is different from the second imaging modality.

14.The system of claim 11, wherein receiving information comprises receiving information regarding the feature of interest.

15.The system of claim 11, wherein the feature of interest comprises a biological feature of interest.

16.The system of claim 15, wherein the biological feature of interest is a vessel or lumen wall.

17.The system of claim 11, wherein the feature of interest comprises a non-biological feature of interest.

18.The system of claim 17, wherein the non-biological feature of interest is a stent.

19.The system of claim 11, wherein detecting the feature of interest comprises initializing a search for the feature of interest based on the combined data set.

20.The system of claim 11, wherein detecting the feature of interest comprises training an algorithm to detect the feature of interest based on the combined data set.

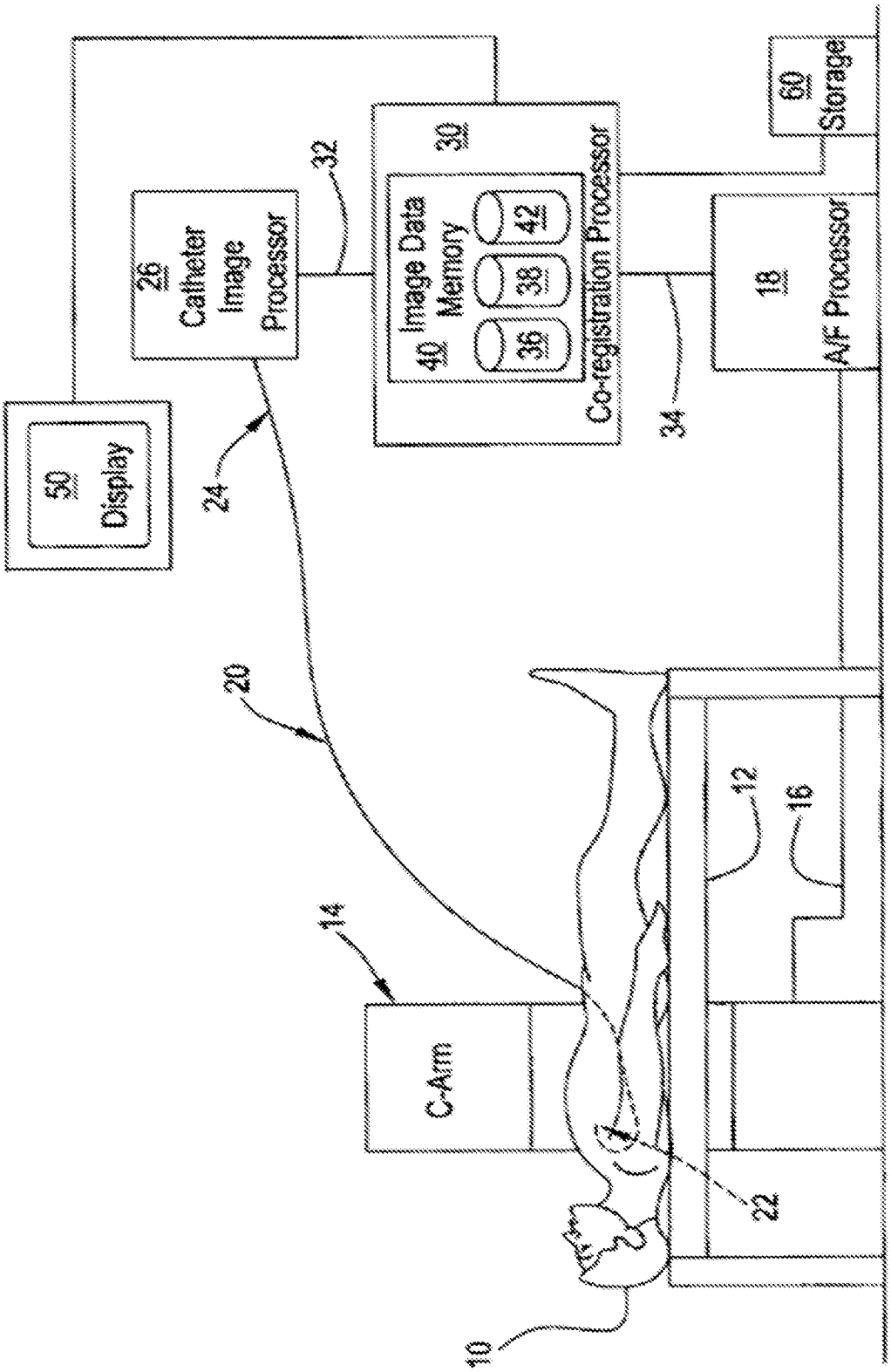

50 Display
26 Catheter Image Processor
32
30
Image Data Memory
40
36
38
42
Co-registration Processor
34
18 A/F Processor
60 Storage
24
20
14
C-Arm
12
16
22
10

FIG. 1

FIG. 2

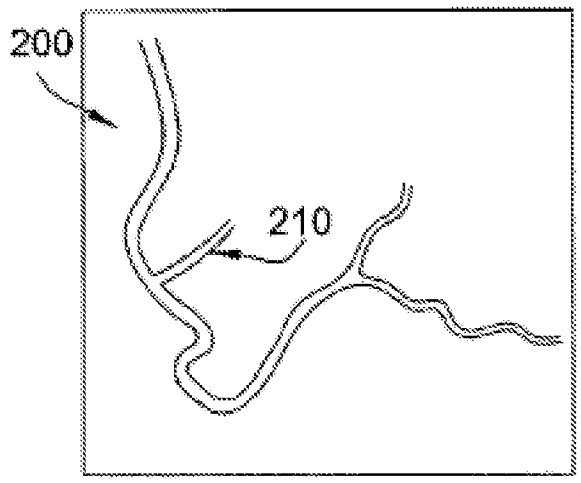


FIG. 3

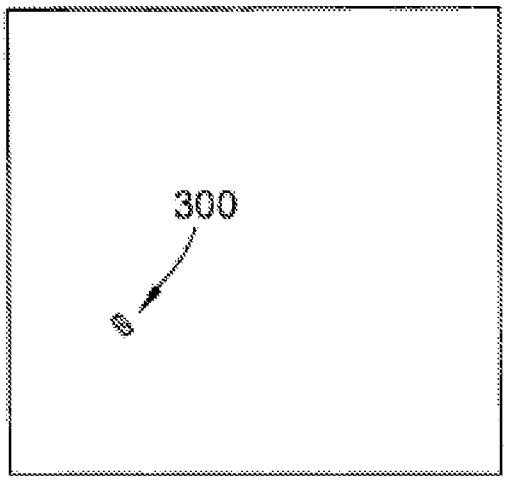
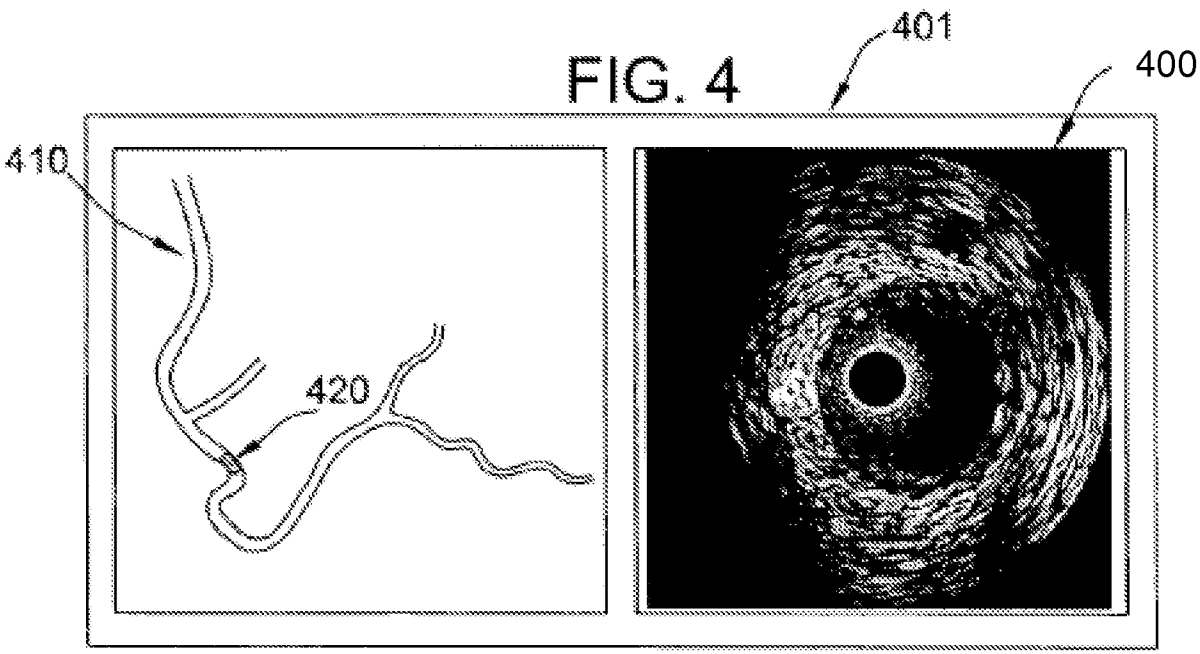


FIG. 4



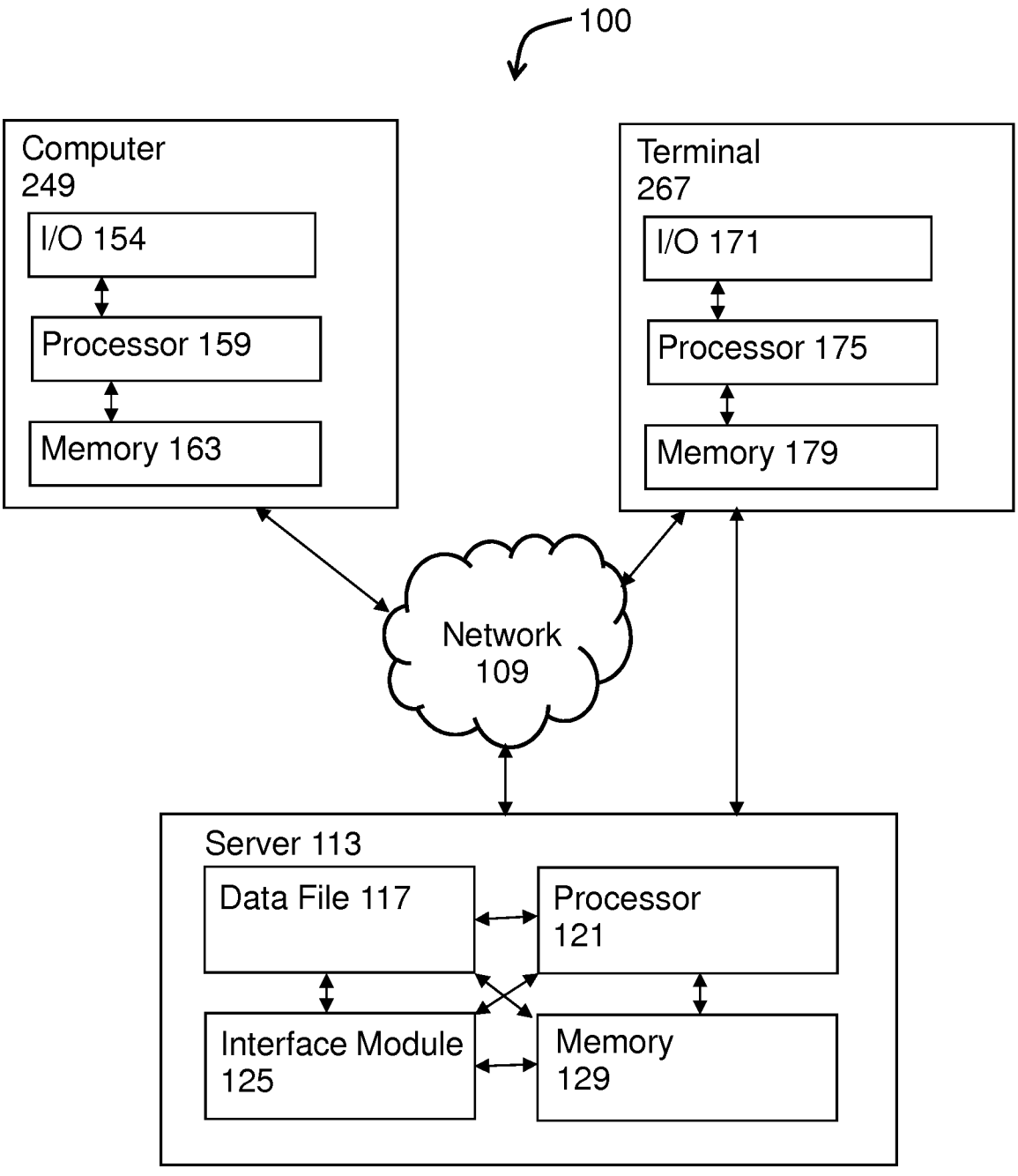

100
Computer
249
I/O 154
Processor 159
Memory 163
Terminal
267
I/O 171
Processor 175
Memory 179
Network
109
Server 113
Data File 117
Processor
121
Interface Module
125
Memory
129

FIG. 5

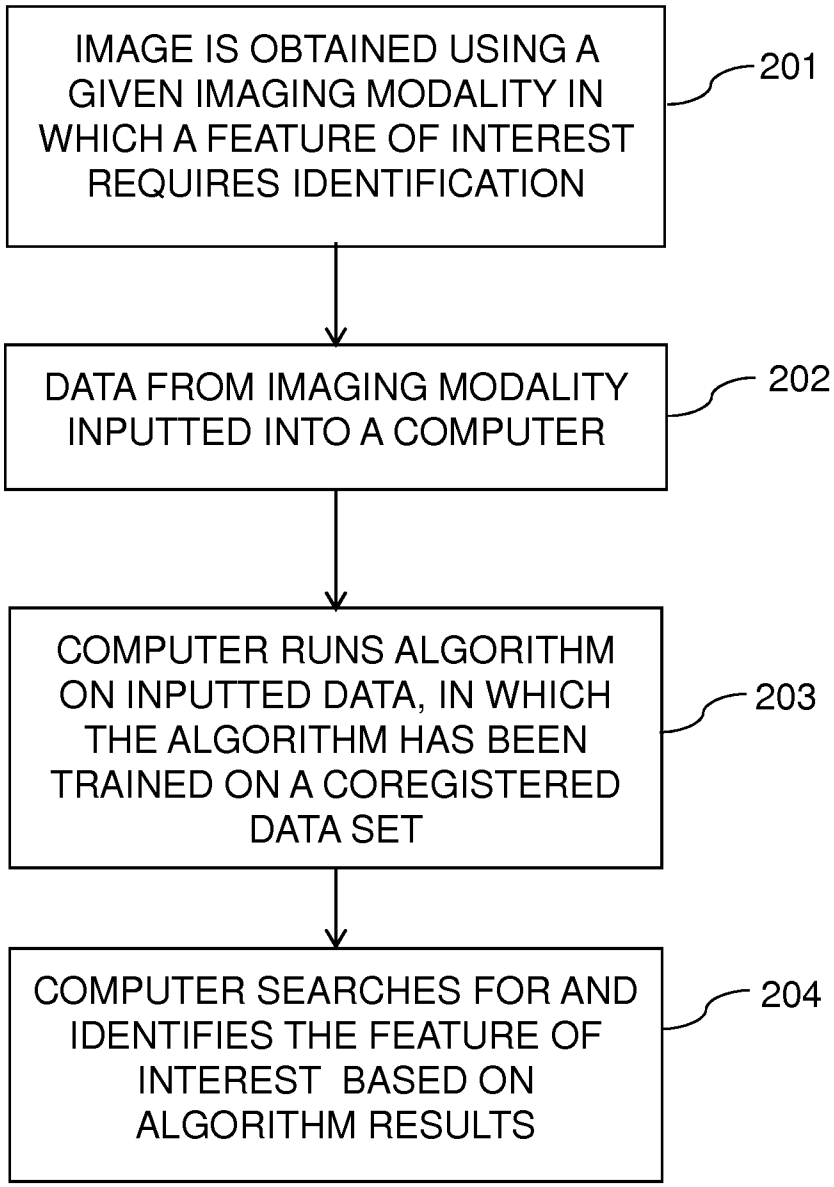


IMAGE IS OBTAINED USING A GIVEN IMAGING MODALITY IN WHICH A FEATURE OF INTEREST REQUIRES IDENTIFICATION
201
DATA FROM IMAGING MODALITY INPUTTED INTO A COMPUTER
202
COMPUTER RUNS ALGORITHM ON INPUTTED DATA, IN WHICH THE ALGORITHM HAS BEEN TRAINED ON A COREGISTERED DATA SET
203
COMPUTER SEARCHES FOR AND IDENTIFIES THE FEATURE OF INTEREST BASED ON ALGORITHM RESULTS
204

FIG. 6

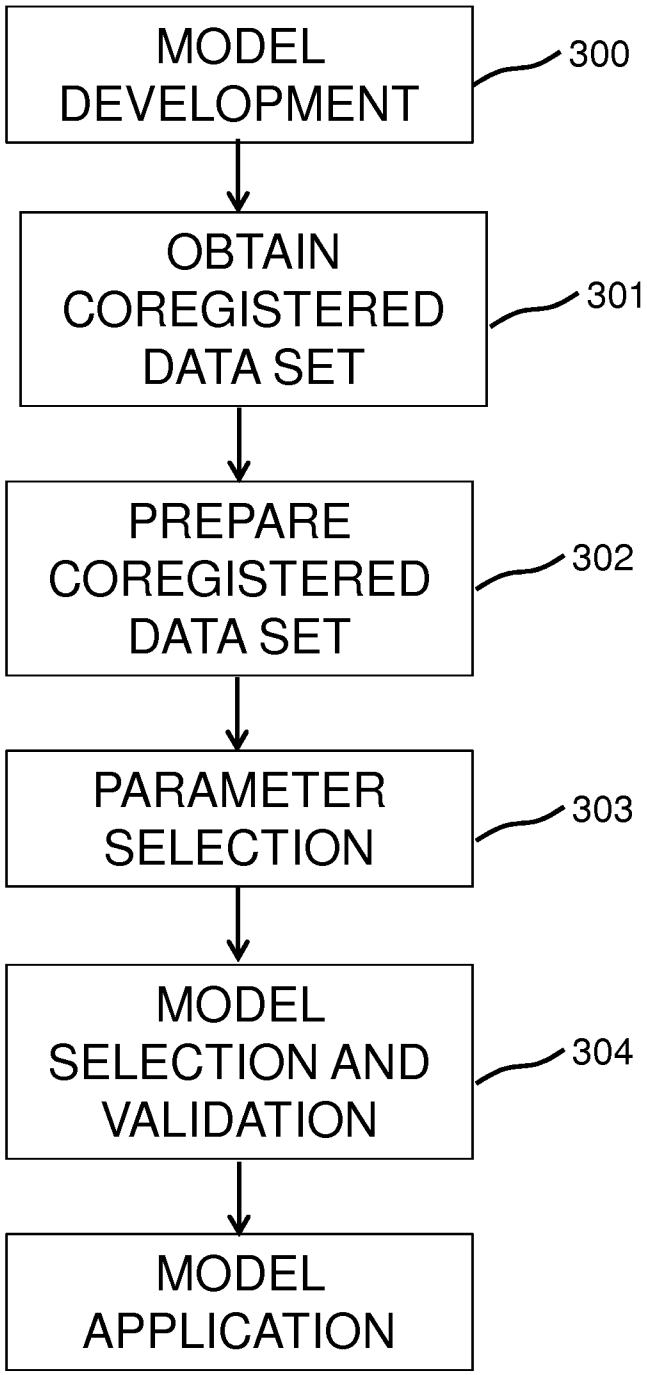

MODEL DEVELOPMENT
300
OBTAIN COREGISTERED DATA SET
301
PREPARE COREGISTERED DATA SET
302
PARAMETER SELECTION
303
MODEL SELECTION AND VALIDATION
304
MODEL APPLICATION

FIG. 7

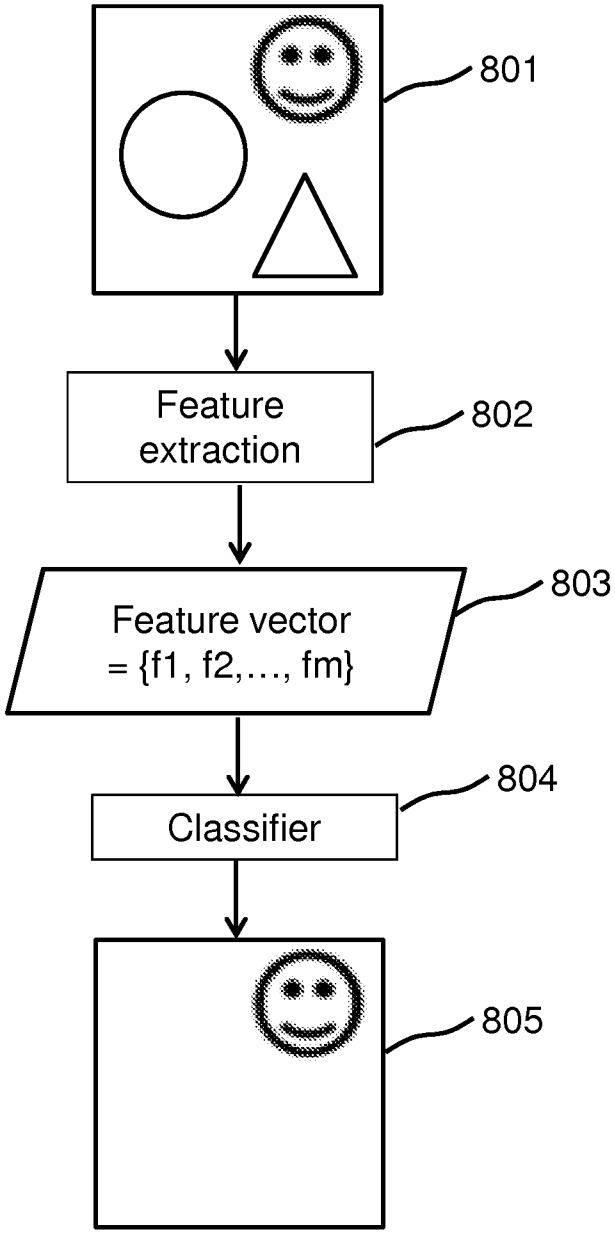

801
Feature extraction
802
Feature vector = {f1, f2,…, fm}
803
Classifier
804
805

FIG. 8

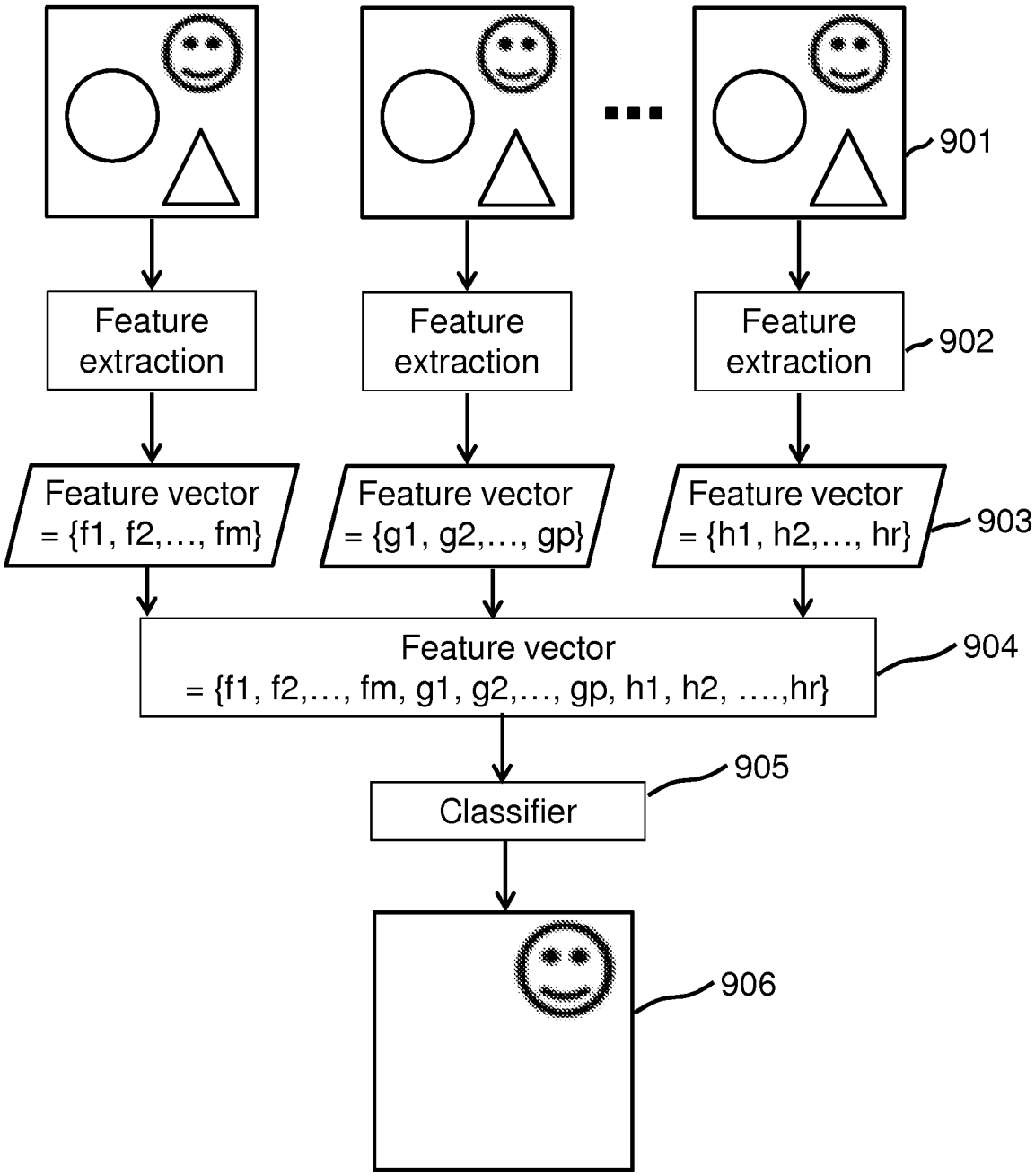

901
Feature extraction
Feature extraction
Feature extraction
902
Feature vector = {f1, f2,…, fm}
Feature vector = {g1, g2,…, gp}
Feature vector = {h1, h2,…, hr}
903
Feature vector = {f1, f2,…, fm, g1, g2,…, gp, h1, h2, ….,hr}
904
905
Classifier
906

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/21659

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G06K 9/40 (2014.01)
USPC - 382/276
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)
USPC: 382/276

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 382/276; 382/293; 382/294 (keyword limited - see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase; Google; Google Scholar, Patents
Terms: image, vascular, modality, type, transform, combine, fusion, coordinates, align, convert, ultrasound, tomography, mri, angiograph, vessel, lumen, search, highlight, stent, registration.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7,356,367 B2 (Liang et al.) 08 April 2008 (08.04.2008), entire document (especially col. 1, ln 35-46; col. 1, ln 60 to col. 2, ln 5; col. 4, ln 62 to col. 5, ln 8; col. 8, ln 53 to col. 9, ln 5; col. 9, ln 48 to col. 10, ln 11)	1-20
A	US 8,126,239 B2 (Sun et al.) 28 February 2012 (28.02.2012), entire document, especially abstract,	1-20
A	US 8,233,681 B2 (Aylward et al.) 31 July 2012 (31.07.2012), entire document.	1-20

☐ 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	Date of mailing of the international search report
25 June 2014 (25.06.2014)	30 JUL 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