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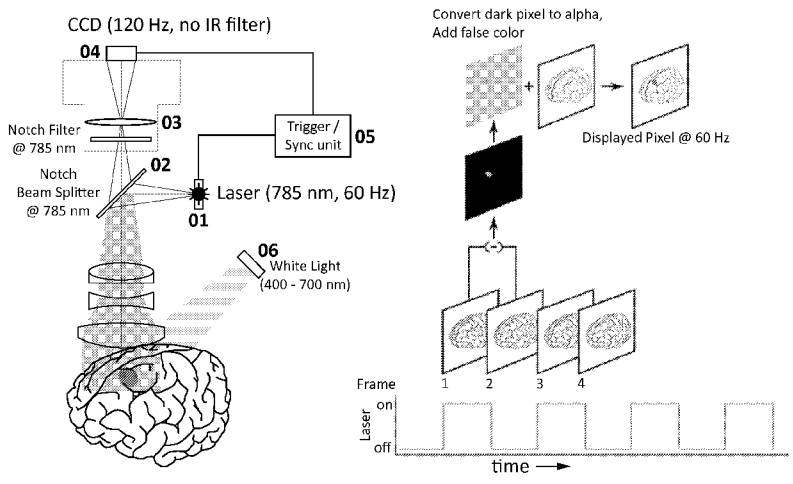
26 February 2015

(54) Title: SYSTEMS AND METHODS FOR RECORDING SIMULTANEOUSLY VISIBLE LIGHT IMAGE AND INFRARED LIGHT IMAGE FROM FLUOROPHORES

Figure 4



(57) Abstract: The invention provides systems and methods for imaging a sample. In various embodiments, the invention provides a system comprising an image sensor, a laser for emitting excitation light for an infrared or near-infrared fluorophore, a visible light source, a notch beam splitter, a notch filter, a synchronization module, an image processing unit, an image displaying unit, and light-conducting channels. In various embodiments, the present invention provides a system comprising an image sensor, a laser for emitting excitation light for an infrared or near-infrared fluorophore, a laser clean-up filter, a notch filter, a white light source, an image processing unit, an image displaying unit, and light-conducting channels. In accordance with the present invention, the image sensor can detect both visible light and infrared light.

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 1/04 (2014.01)
USPC - 600/109
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) - A61B 1/04, 1/00; G01J 3/44 (2014.01)
USPC - 600/101, 109, 111, 129; 356/301, 326, 323

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61B 1/05, 1/042, 1/00193 (2014.09) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Orbit, Google Patents, ProQuest
Search terms used: image sensor, sample, laser, notch filter, fluorophore, infrared

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,689,333 A (BATCHELDER et al) 18 November 1997 (18.11.1997) entire document	1-30, 67-69
Y	US 2013/0041226 A1 (MCDOWALL) 14 February 2013 (14.02.2013) entire document	1-30, 67-69
Y	US 2006/0226375 A1 (MARUO) 12 October 2006 (12.10.2006) entire document	9
Y	US 2012/0104280 A1 (MANIAN) 03 May 2012 (03.05.2012) entire document	15, 17-18
Y	US 6,075,592 A (BANERJEE et al) 13 June 2000 (13.06.2000) entire document	16
Y	US 2002/0115908 A1 (FARKAS et al) 22 August 2002 (22.08.2002) entire document	22-25
Y	US 2012/0268573 A1 (SCHONBORN et al) 25 October 2012 (25.10.2012) entire document	23-25
Y	US 2009/0050806 A1 (SCHMIDT et al) 26 February 2009 (26.02.2009) entire document	27
Y	US 2011/0261179 A1 (FOMITCHOV) 27 October 2011 (27.10.2011) entire document	28-30
A	US 2012/0123205 A1 (NIE et al) 17 May 2012 (17.05.2012) entire document	1-30, 67-69
A	US 2002/0156380 A1 (FELD et al) 24 October 2002 (24.10.2002) entire document	1-30, 67-69
A	US 2002/0113210 A1 (TREADO et al) 22 August 2002 (22.08.2002) entire document	1-30, 67-69

☐ 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
06 December 2014	24 DEC 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: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/035203

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 66, 79-84
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
See the last page

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-30, 67-69

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/035203

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.
Group I, claims 1-30, 67-69, drawn to an imaging system for imaging a sample.
Group II, claims 31, 60-65, 70-72, 76-78, drawn to an imaging system for imaging a sample comprising an image processing unit to process sensor signals to generate image frames, an image displaying unit to display images based on the image frames generated from the image processing unit.
Group III, claims 32-59, 61-65, 73-75, drawn to an imaging system for imaging a sample comprising a synchronization module to synchronize the image sensor with the laser and visible light, whereby a single sensor signal is synchronized to a single on or off status of the laser.
Group IV, claims 85-111, drawn to computer implemented method for capturing and processing images and for smooth image display comprising instructions for utilizing parallel process software coding; transferring a raw image; and de-mosaicing the raw image to the one or more processors.
The inventions listed as Groups I, II, III or IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of the Group I invention: a laser, laser clean-up filter, a notch filter and while light source as claimed therein is not present in the invention of Groups II, III or IV. The special technical feature of the Group II invention: an image processing unit to process sensor signals to generate image frames, wherein the image processing unit is connected to the image sensor, wherein at least one white light frame (WLF) is generated when the sample receives only visible light, wherein at least one stray light frame (SLF) is generated when the sample receives neither visible light nor the excitation light, wherein one or more near infrared frames (NIFs) are generated when the sample receives only excitation light, wherein the image processing unit subtracts the SLF from each NIF and then adds together all SLF-subtracted NIFs to generate a final NIF, wherein the image processing unit false colors the final NIF, and wherein the image processing unit adds the false colored final NIF to the WLF to generate a composite image frame of visible light and infrared light, an Image displaying unit to display images based on the image frames generated from the image processing unit, wherein the image displaying unit is connected to the image processing unit as claimed therein is not present in the invention of Groups I, III or IV. The special technical feature of the Group III invention: a synchronization module to synchronize the image sensor with the laser and visible light, whereby a single sensor signal is synchronized to a single on or off status of the laser as claimed therein is not present in the invention of Groups I, II or IV. The special technical feature of the Group IV invention: utilizing parallel process software coding; transferring a raw image; and de-mosaicing the raw image to the one or more processors as claimed therein is not present in the invention of Groups I, II or III.

Groups I, II, III and IV lack unity of invention because even though the inventions of these groups require the technical feature of an imaging system for imaging a sample comprising an infrared or near-infrared
fluorophore, comprising: an image sensor to detect visible light and infrared light and generate sensor signals; a laser to emit an excitation light for the infrared or near-infrared fluorophore; a laser clean-up filter in the light path from the laser to the sample, whereby the laser clean-up filter narrows the wavelength band of the excitation light to the peak absorption band of the infrared or near-infrared fluorophore, and whereby the narrowed excitation light excites the infrared or near-infrared
fluorophore in the sample to emit an emission light; a notch filter in the light path from the sample to the image sensor, whereby the notch filter blocks the excitation light; and a white light source to emit a light comprising visible light, this technical feature is not a special technical feature as it does not make a contribution over the prior art.
Specifically, US 5,689,333 (BATCHELDER et al.) teaches an imaging system for imaging a sample (focusing a two dimensional image of an illumination area on the sample 14 onto the CCD, col. 5, lines 3-5; thus fig.1 shows an imaging system for imaging a sample 14), comprising: an image sensor to detect Raman light and generate sensor signals (the transmitted Raman spectrum is taken via various optical components and focused by a lens 34 onto a two-dimensional photo-detector array in the form of CCD 12. A computer 120 acquires data from the CCD 12 for subsequent data processing, col. 3, lines 8-14); a laser to emit an excitation light for the sample (the laser light is reflected through 90 degrees by the filter arrangement 18 and passed via a further mirror 46 and focused to a small spot on a sample 14, col. 2, lines 50-53); a laser clean-up filter in the light path from the laser to the sample, whereby the laser clean-up filter adjusts the wavelength band of the excitation light, and whereby the excitation light excites the sample to emit an emission light (a laser input beam 10 passes through a lens system 40, which may include a spatial filter (e.g., pinhole 41) to improve beam quality. The spatial filter removes unwanted imperfections in the original laser beam caused by reflections, which would cause interference effects when the beam is subsequently focused to a spot on a sample, col. 2, lines 39-45. The light scattered by the sample from the illuminated spot on the surface, col. 3, lines 4-5; thus fig.1 shows a laser clean-up filter (spatial filter 41 is considered a "laser clean up filter") in the light path from the laser (laser input 10) to the sample 14, whereby the laser clean-up filter 41 adjusts the wavelength band of the excitation light, and whereby the excitation light excites the sample 14 to emit an emission light); a notch filter in the light path from the sample to the image sensor, whereby the notch filter blocks the excitation light (the filter 18 transmits the Raman spectrum but rejects Rayleigh Scattered light having the same frequency as the input laser beam, col. 3, lines 6-8. These filters are also holographic notch filters, col. 3, lines 40-49; thus fig.1 shows a notch filter 18 in the light path from the sample 14 to the image sensor 12, whereby the notch filter blocks the excitation light (input laser beam)); and a white light source to emit a light comprising visible light (a source 50 of white light above the mirror 46 for illuminating the sample, col. 2, lines 58-59). Batchelder et al. does not teach the sample comprising an infrared or near-infrared fluorophore, the image sensor to detect visible light and infrared light, and the laser clean-up filter narrows the wavelength band of the excitation light to the peak absorption band of the infrared or near-infrared fluorophore.
US 2013/0041226 A1 (MCDOWALL) teaches that the sample comprising an infrared or near-infrared fluorophore (exciting fluorescence in tissue (sample) 203. Narrow band light from the fluorescence excitation source is used to excite tissue specific near infrared emitting fluorophores, para. 0082), the image sensor to detect visible light and infrared light (a visible image of the scene and one or more fluorescence images in the scene are acquired by image capture units 225L, 225R, para. 0076. Narrow band light from the fluorescence excitation source is used to excite tissue specific near infrared emitting fluorophores so that fluorescence images of specific features within tissue 203 are acquired by image capture units 225L, 225R, para. 0082), and it is well known in the art that the excitation light from the narrow band light is used to excite tissue-specific near infrared emitting fluorophores (para. 0082). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the imaging system of Batchelder by including the sample comprising an infrared or near-infrared fluorophore, the image sensor to detect visible light and infrared light, and the laser clean-up filter narrowing the wavelength band of the excitation light to the peak absorption band of the infrared or near-infrared fluorophore so as to provide fluorescence images of specific features within tissue to be acquired by image capture units (McDowall, para. 0082), since adjusting the laser clean up filter as such, where needed for operation, involves only routine skill in the art.

Since none of the special technical features of the Group I, II, III or IV inventions are found in more than one of the inventions, unity of invention is lacking.