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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 February 2012 (02.02.2012)

PCT

(10) International Publication Number
WO 2012/016242 A3

(51) International Patent Classification:
G06T 5/30 (2006.01) *G06T 7/00* (2006.01)

(21) International Application Number:
PCT/US2011/046149

(22) International Filing Date:
1 August 2011 (01.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/400,642	30 July 2010 (30.07.2010)	US
61/400,657	30 July 2010 (30.07.2010)	US
61/455,988	28 October 2010 (28.10.2010)	US
61/456,009	28 October 2010 (28.10.2010)	US

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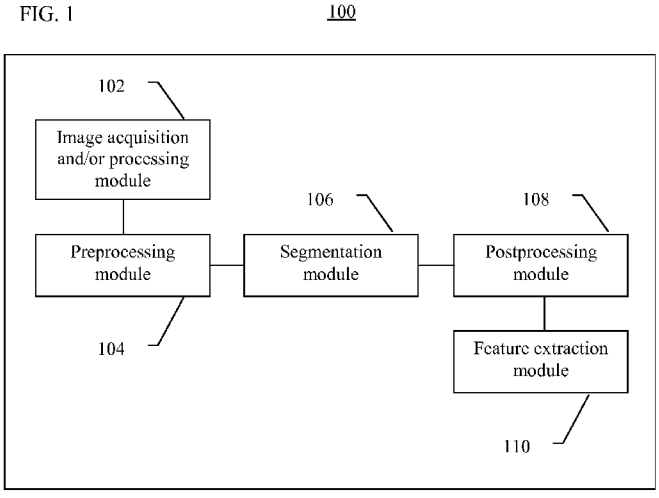
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, 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, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: SYSTEMS AND METHODS FOR SEGMENTATION AND PROCESSING OF TISSUE IMAGES AND FEATURE EXTRACTION FROM SAME FOR TREATING, DIAGNOSING, OR PREDICTING MEDICAL CONDITIONS

FIG. 1



(57) Abstract: Apparatus, methods, and computer-readable media are provided for segmentation, processing (e.g., preprocessing and/or postprocessing), and/or feature extraction from tissue images such as, for example, images of nuclei and/or cytoplasm. Tissue images processed by various embodiments described herein may be generated by Hematoxylin and Eosin (H&E) staining, immunofluorescence (IF) detection, immunohistochemistry (IHC), similar and/or related staining processes, and/or other processes. Predictive features described herein may be provided for use in, for example, one or more predictive models for treating, diagnosing, and/or predicting the occurrence (e.g., recurrence) of one or more medical conditions such as, for example, cancer or other types of disease.

WO 2012/016242 A3

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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))*

(88) Date of publication of the international search report:
18 May 2012

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/046149

A. CLASSIFICATION OF SUBJECT MATTER
INV. G06T5/30 G06T7/00
ADD.

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)
G06T

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, COMPENDEX, INSPEC, IBM-TDB, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2006/257013 A1 (RAMM PETER [CA] ET AL) 16 November 2006 (2006-11-16) abstract paragraph [0002] paragraph [0220] - paragraph [0222] figure 3 -----	1,2,11, 14,15 3,4
X Y	WAEHLBY C ET AL: "ALGORITHMS OF CYTOPLASM SEGMENTATION OF FLUORESCENCE LABELLED CELLS", ANALYTICAL CELLULAR PATHOLOGY, ELSEVIER SCIENCE, AMSTERDAM, NL, vol. 24, no. 2/03, 1 January 2002 (2002-01-01), pages 101-111, XP008017746, ISSN: 0921-8912 section 2.1; the whole document -----	1,14,15 3,4
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* 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 document 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
24 November 2011	04/04/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/046149

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TEVEROVSKIY M ET AL: "Automated localization and quantification of protein multiplexes via multispectral fluorescence imaging", BIOMEDICAL IMAGING: FROM NANO TO MACRO, 2008. ISBI 2008. 5TH IEEE INTERNATIONAL SYMPOSIUM ON, IEEE, PISCATAWAY, NJ, USA, 14 May 2008 (2008-05-14), pages 300-303, XP031271036, ISBN: 978-1-4244-2002-5 section 2	3,4
X	US 6 577 762 B1 (SEEGER MAURITIUS [GB] ET AL) 10 June 2003 (2003-06-10) column 9 - column 10 figure 11 claim 1	1,2,12, 13
X	JP 2003 167529 A (SEIKO EPSON CORP) 13 June 2003 (2003-06-13) paragraphs [0010], [0022]	1,2,12, 13
A	US 2008/267497 A1 (FAN JIAN [US]) 30 October 2008 (2008-10-30) the whole document	1-15
X,P	PETER AJEMBA ET AL: "Integrated segmentation of cellular structures", PROCEEDINGS OF SPIE, 1 January 2011 (2011-01-01), pages 79620I-79620I-10, XP055012179, ISSN: 0277-786X, DOI: 10.1117/12.876722 the whole document	1-15
X,P	US 2011/110595 A1 (KIM DO-HYEON [KR] ET AL) 12 May 2011 (2011-05-12) the whole document	1,2,12, 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/046149

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.:
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 additional sheet

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 an 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.:

1-15

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-15

   Reducing non-uniform variations in intensity in a tissue image

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2. claims: 16-27

   Binarization of a tissue image

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3. claims: 28, 29, 31-36

   Processing a segmented image of cytoplasm

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4. claim: 30

   Processing a segmented image of nuclei

   ---

5. claims: 37-41

   Removing artifacts from a segmented image of nuclei

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6. claims: 42-50, 56

   Separating epithelial/gland units within a tissue/nulcei image

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7. claims: 51-55

   Refining an epithelial unit segmentation within a segmented tissue image

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8. claims: 57-59

   Enhancing ridges formed by cytoplasm membranes around an outer boundary of touching or almost touching cytoplasm within a tissue image

   ---

9. claims: 60-72

   Segmenting gland rings within a tissue image

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10. claims: 73-78

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Localizing and quantifying biomarker signal within a tissue image

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11. claims: 79-92, 107-114

Predicting occurrence of a medical condition

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12. claims: 93-96

Extracting one or more texture features from an image of tissue

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13. claims: 97-106

Assessing stability of a segmentation process using a tissue image

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14. claims: 115-117

Detecting lumens within a tissue image

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/046149

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006257013 A1	16-11-2006	US 2006257013 A1	16-11-2006
		US 2009074283 A1	19-03-2009
		US 2010254590 A1	07-10-2010
US 6577762 B1	10-06-2003	NONE	
JP 2003167529 A	13-06-2003	JP 4320990 B2	26-08-2009
		JP 2003167529 A	13-06-2003
US 2008267497 A1	30-10-2008	CN 101689300 A	31-03-2010
		DE 112008001052 T5	04-03-2010
		JP 2010525486 A	22-07-2010
		US 2008267497 A1	30-10-2008
		WO 2008134000 A1	06-11-2008
US 2011110595 A1	12-05-2011	KR 20110051900 A	18-05-2011
		US 2011110595 A1	12-05-2011