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A systematic review on the evaluation and characteristics of computer-aided diagnosis systems

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Abstract **Introduction**: One of the challenges in developing Computer-Aided Diagnosis (CAD) systems is their accurate and comprehensive assessment. This paper presents the conduction and results of a systematic review (SR) that aims to verify the state of the art regarding the assessment of CAD systems. This survey provides a general analysis of the current status of the design, development and assessment of such systems and includes discussions on the most used metrics and approaches that could be utilized to obtain more objective evaluation methods. **Methods**: The SR was conducted using the scientific databases, ACM Digital Library, IEEE Xplore Digital Library, ScienceDirect and Web of Science. Inclusion and exclusion criteria were defined and applied to each retrieved work to select those of interest. From 156 studies retrieved, 100 studies were included. **Results**: There is a number of abnormalities that have been used for the development of CAD systems. Images from computed tomographies and mammographies are the most encountered types of medical images. Additionally, a number of studies used public databases for CAD evaluations. The main evaluation metrics and methods applied to CAD systems include sensitivity, accuracy, specificity and receiver operating characteristic (ROC) analyses. In the assessed CAD systems that used the segmentation method, 30.0% applied the overlap measure. **Discussion**: There remain several topics to explore for the assessment of CAD schemes. While some evaluation metrics are traditionally used, they require a prior knowledge of case characteristics to test CAD systems. We were not able to identify articles that use software testing to evaluate CAD systems. Thus, we realize that there is a gap between CAD assessments and traditional practices of software engineering. However, the scope of this research is limited to scientific and academic works and excludes commercial interests. Finally, we discuss potential research studies within this scope to create a more objective and efficient evaluation of CAD systems.

Keywords CAD evaluation, Classification, Computer-aided diagnosis, Detection, Medical image, Segmentation.

Introduction

Computer-Aided Diagnosis (CAD) schemes are computer systems aiming at providing second opinions to physicians to aid in diagnoses (Doi, 2007). These systems compute outputs based on information from diverse sources, primarily from medical images captured using various methods. According to van Ginneken et al. (2010), CAD has become the most active field of research in medical imaging. Further, Doi (2006) showed that CAD systems provide consistent interpretations of medical images to improve the precision of a diagnosis.

The assessment of CAD schemes is one of the major difficulties encountered in their development. Because results can vary depending on the used set of images, it is not an easy task to determine the effectiveness of a particular technique. To ascertain the feasibility of a technique, tests should be conducted with a set of images that preferably have varied acquisition characteristics. Additionally, this image set should meet the requirements of the purpose of the technique, i.e., they should contain the structures sought by the computer system. This entails a collaborative effort with hospitals and clinics to perform detailed and thorough analyses to obtain appropriate medical images and their respective reports. The cataloging of these images based on their characteristics allow for their fast and accurate retrieval.

This paper presents a systematic review (SR) aiming to verify the state of the art regarding the assessment of CAD systems. Additionally, we analyzed data from the included studies, such as computational techniques employed in the development of CAD schemes, abnormalities investigated and modalities of the most explored medical imaging. Thus, this survey made possible a general analysis of the current scope regarding the design, development and assessment of such systems.

Overviews on the development and trends of CAD schemes have been presented by Doi (2007) and Shiraishi et al. (2009). Doi (2007) carried out a historical review regarding the development of CAD schemes. Examples of works that explored different modalities of medical imaging were also presented to

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aid in diagnosing several abnormalities, such as lung nodules, vertebral fractures and intracranial aneurysms. Doi also discussed the potential of such schemes for applications in clinical routines. Shiraishi et al. (2009) presented a review on the application of analyses using Receiver Operating Characteristic (ROC) curves to assess CAD systems. The review included studies published in Radiology Journal between 1997 and 2006. The review also analyzed the participation of human observers in the assessment processes and identified the most explored medical imaging modalities.

In our study, the presented unique systematic review is based on a set of criteria characterizing the differences and relevance between results, as listed below:

- A comprehensive selection of scientific databases as reference sources, allowing access to diverse publications in the field (these databases were selected after carrying out an exploratory study that defined relevant research sources);
- A definition and disclosure of an SR protocol that was strictly followed during the review (this protocol permitted a reproducible review and audited the used criteria); and

An analysis of results taking into account each automated task to aid individual diagnoses (i.e., segmentation, detection and classification of abnormalities and regions of interest).

In addition to this introductory section, the paper is organized as follows. The "Methods" section presents concepts about the SR, the protocol used and the process of conducting the review. The "

Results and discussion" section presents and discusses the results.

Methods

The systematic review is a rigorous methodology of bibliographic research that aims to identify primary and secondary studies related to a particular research topic. It permits the assessment and interpretation of all relevant research on a particular issue or topic of interest (Kitchenham, 2004).

According to Biolchini et al. (2007) and Kitchenham (2004), an SR is carried out in three well-defined phases: planning, conduction and analysis of results. In the planning phase, a protocol is defined specifying research questions and the methodology to be employed in the conduction of the review. Furthermore, this protocol defines purposes for the SR, reference sources, criteria for the inclusion or exclusion of primary studies, keywords and other topics of interest. In the conduction phase, the bibliographic research is carried out. In this phase, studies are selected according to the defined inclusion and exclusion criteria. Finally, in the analysis of results, the data extraction is performed, and the results are compared.

A major difference between an SR and the non-systematic review of the literature is the fact that the establishment of a protocol allows the SR to be reproduced and audited. Other researchers can follow the same protocol and assess the methods used for the case at issue (Biolchini et al., 2007). The following subsections describe each of the previously cited phases applied in the SR carried out in the present work.

Planning

First, research questions are defined:

- What are the methodologies currently applied for the assessment of CAD systems based on medical imaging?
- What are the modalities of medical imaging, abnormalities and computational techniques involved in the development of CAD systems?
- What are the advantages and limitations presented by the assessment methodologies employed in CAD systems?

An exploratory analysis on CAD was carried out over several scientific databases. This preliminary survey aided in selecting reference sources and the definition of the keywords used in the SR. Based on our experiences with journals, we consulted databases that traditionally published articles on the subject. The following databases were selected:

- *ACM Digital Library* (ACM)
- *IEEE Xplore Digital Library* (IEEE)
- *ScienceDirect* (SD)
- *Web of Science* (WS)

From the defined keywords of the protocol, queries for papers on journals or proceedings of scientific conferences were carried out in the selected databases. Only recent studies (published since 2006) were considered for assessing the state of the art of CAD.

The selection of acknowledged reference sources in the field made it possible to retrieve a significant number of studies on CAD. Moreover, defining adequate criteria for the inclusion and exclusion of works focused the sources to the relevant subject matter. A composition of terms was used to initially narrow the scope of the reference sources. These terms had to be present in the title, abstract or keywords to qualify a source (these indices were searchable by means of advanced search tools available for each database). The defined terms were as follows:

(evaluation OR testing OR assessment)
AND
("computer-aided diagnosis system" OR "computer-aided diagnosis scheme" OR "computer-assisted diagnosis system" OR "computer-assisted diagnosis scheme" OR "diagnosis support system" OR "diagnostic support system")

Table 1 presents the compositions of terms translated for each of the search engines of the consulted databases.

To select only relevant papers for the subject of study, we defined the inclusion and exclusion criteria. We included only studies that met at least one of the inclusion criteria and none of the exclusion criteria.

Sources that met the defined inclusion criteria had to:

(a) present or discuss concepts, criteria and methodologies to assess CAD systems whose outputs are presented as images or use images processed in a way to enable diagnoses;
(b) apply a specific methodology in the assessment of some CAD system with the characteristics mentioned in the first inclusion criterion; or
(c) present concepts or historical reviews on CAD.

In turn, excluded sources that met all the defined exclusion criteria had to:

(d) be similar, in content and results, with other studies by the same authors retrievable from any of the consulted databases;
(e) have a publication year outside the specified deadline (i.e., earlier than 2006); and

Table 1. Composition of terms used in searches.

Source	Search tool and options	Refinement by year	Terms compositions
ACM	Advanced search Custom search string	Yes	(evaluation or assessment or testing or Keywords:evaluation or Keywords:assessment or Keywords:testing) and ("computer-aided diagnosis system" or "computer-aided diagnosis scheme" or "computer-assisted diagnosis system" or "computer-assisted diagnosis scheme" or "diagnosis support system" or "diagnostic support system" or Keywords:"computer-aided diagnosis system" or Keywords:"computer-aided diagnosis scheme" or Keywords:"computer-assisted diagnosis system" or Keywords:"computer-assisted diagnosis scheme" or Keywords:"diagnosis support system" or Keywords:"diagnostic support system")
IEEE	Command search Search: metadata only	Yes	("Document Title":evaluation OR "Abstract":evaluation OR "Author Keywords":evaluation OR "Document Title":assessment OR "Abstract":assessment OR "Author Keywords":assessment OR "Document Title":testing OR "Abstract":testing OR "Author Keywords":testing) AND ("Document Title":"computer-assisted diagnosis scheme" OR "Abstract":"computer-assisted diagnosis scheme" OR "Author Keywords":"computer-assisted diagnosis scheme" OR "Document Title":"computer-assisted diagnosis system" OR "Abstract":"computer-assisted diagnosis system" OR "Author Keywords":"computer-assisted diagnosis system" OR "Document Title":"computer-aided diagnosis system" OR "Abstract":"computer-aided diagnosis system" OR "Author Keywords":"computer-aided diagnosis system" OR "Document Title":"computer-aided diagnosis scheme" OR "Abstract":"computer-aided diagnosis scheme" OR "Author Keywords":"computer-aided diagnosis scheme" OR "Document Title":"diagnosis support system" OR "Abstract":"diagnosis support system" OR "Author Keywords":"diagnosis support system" OR "Document Title":"diagnostic support system" OR "Abstract":"diagnostic support system" OR "Author Keywords":"diagnostic support system")
SD	Advanced search	Yes	pub-date > 2005 and TITLE-ABSTR-KEY(evaluation OR testing OR assessment) and TITLE-ABSTR-KEY("computer-aided diagnosis system" OR "computer-aided diagnosis scheme" OR "computer-assisted diagnosis scheme" OR "computer-assisted diagnosis system" OR "diagnosis support system" OR "diagnostic support system")
WS	Document type = (ARTICLE OR MEETING)	Yes	Topic: (evaluation OR testing OR assessment) AND Topic: ("computer-aided diagnosis system" OR "computer-aided diagnosis scheme" OR "computer-assisted diagnosis scheme" OR "computer-assisted diagnosis system" OR "diagnosis support system" OR "diagnostic support system")

(f) not be fully available in the consulted databases or in any other database accessible on the Internet.

Conduction and data extraction

The searches were carried out between April and June 2014. In total, 156 studies were retrieved. As a whole, 100 studies (64.10%) were included, 96 of which had CAD schemes and the employed assessment methodologies. Four papers contained conceptual contents as described in the subsection "*Review and theoretical papers*".

Every conduction stage of the SR was duly documented based on the models proposed in Biolchini et al. (2007) and Kitchenham (2004). The produced documents and the tools used are described below.

Conduction form: One form was produced for each consulted database. They document all the relevant information of the search: access dates, a composition of terms used, a list of retrieved studies and their satisfied inclusion criteria and other observations.

Data extraction form: For each included study, in addition to the bibliographic and reference information, a summary of the study and documented topics of interest were included. The main topics of interest extracted included: the purpose of the system used/proposed, assessment method of the employed CAD, modality and number of images/cases used in the test, main tests and results and other information relevant research.

Figure 1 shows a flow diagram, based on Liberati et al. (2009), which summarizes the selection of the studies.

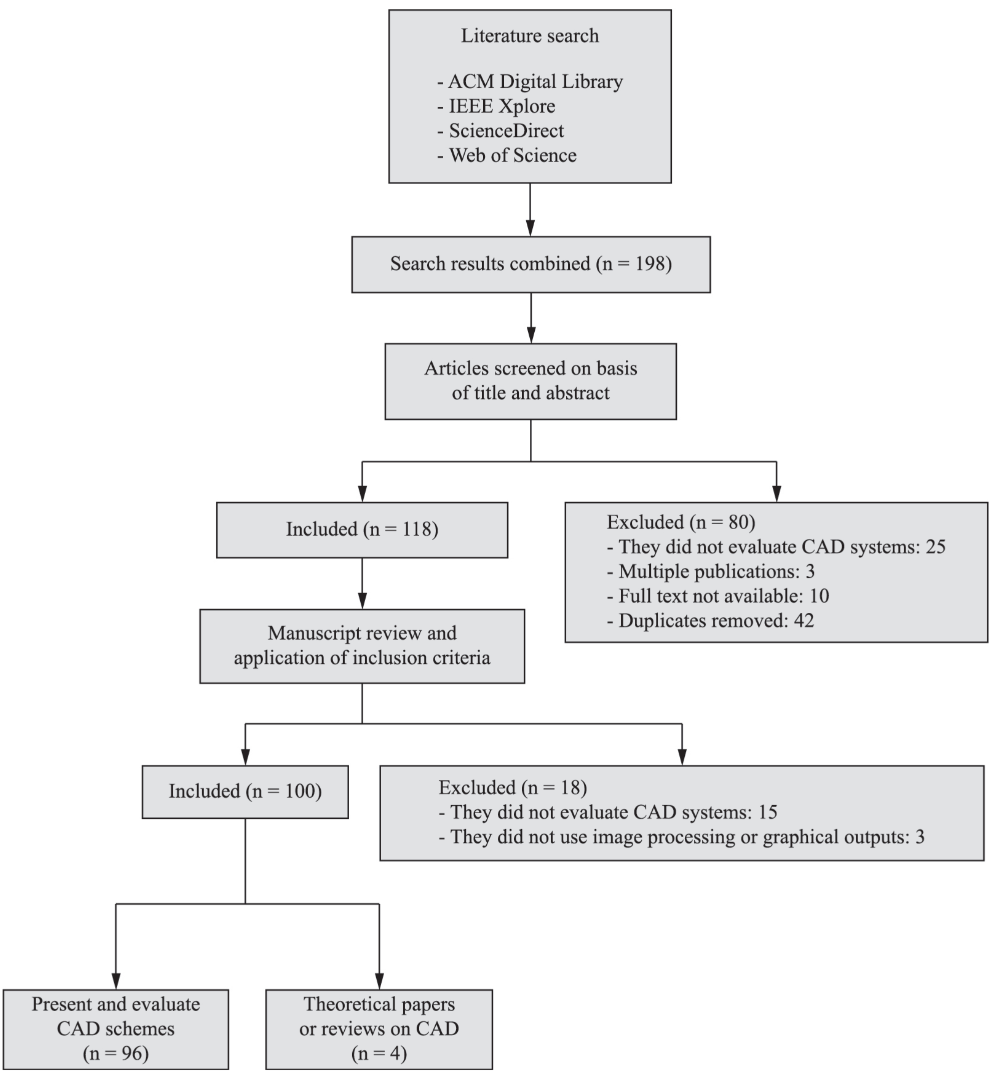

Figure 1. Flow diagram summarizing the selection studies stage.

Table 2 shows the studies included, and their satisfied inclusion criteria. We retrieved studies published in scientific journals, conference proceedings and other collections of articles. In particular, a significant variety of medical publications, computational intelligence, and imaging processing and analyses (other than pattern recognition) were observed. Table 3, Table 4 and Table 5 show the

Table 2. Criteria met by each included paper.

Reference	Criteria	Reference	Criteria
Al-Absi et al. (2012)	(b)	López et al. (2011)	(a) (b)
Ampeliotis et al. (2007)	(b)	Muramatsu et al. (2013)	(b)
Ashwin et al. (2012)	(a) (b)	Markkongkeaw et al. (2013)	(b)
Barhoumi et al. (2007)	(b)	Martinez-Murcia et al. (2014)	(b)
Beuren et al. (2012)	(a) (b)	Mironică et al. (2011)	(b)
Bevilacqua (2013)	(a) (b)	Miyaki et al. (2013)	(b)
Bhooshan et al. (2011)	(b)	Moon et al. (2011)	(b)
Chan (2010)	(b)	Mumcuoglu et al. (2011)	(a) (b)
Chang et al. (2006)	(b)	Muramatsu et al. (2013)	(b)
Charbonnier et al. (2013)	(a) (b)	Nagata et al. (2013)	(b)
Charisis et al. (2013)	(b)	Nava et al. (2014)	(b)
Cheng et al. (2012)	(a) (b)	Odeh et al. (2006)	(a) (b)
David et al. (2008)	(b)	Osman et al. (2009)	(a) (b)
Elizabeth et al. (2012)	(a) (b)	Pietka et al. (2010)	(a) (b)
Endo et al. (2012)	(a) (b)	Pietka et al. (2011)	(a) (c)
Filipczuk et al. (2013)	(b)	Raja et al. (2007)	(b)
García-Orellana et al. (2008)	(b)	Raja et al. (2010)	(b)
Garnavi et al. (2011)	(a) (b)	Ramírez et al. (2009)	(b)
Garnavi et al. (2012)	(b)	Ramos et al. (2012)	(a) (b)
Gedik and Atasoy (2013)	(a) (b)	Retter et al. (2013)	(b)
Geetha et al. (2008)	(a) (b)	Roberts et al. (2010)	(b)
Giannakopoulou et al. (2010)	(b)	Sanchez et al. (2011)	(a) (b)
Gomathi and Thangaraj (2010)	(b)	Sasaki et al. (2010)	(b)
Gopinath and Shanthi (2013)	(a) (b)	Sato et al. (2011)	(a) (b)
Grana et al. (2011)	(b)	Schilham et al. (2006)	(a) (b)
Gruszauskas et al. (2008)	(a) (b)	Segovia et al. (2012)	(a) (b)
Gruszauskas et al. (2009)	(b)	Shen et al. (2007)	(a) (b)
Haindl et al. (2007)	(b)	Shilaskar and Ghatol (2013)	(a) (b)
Hatanaka et al. (2011)	(b)	Shiraishi et al. (2009)	(a) (c)
He et al. (2011)	(b)	Song et al. (2010)	(a) (b)
Hebert et al. (2012)	(b)	Streba et al. (2012)	(b)
Huang et al. (2007)	(b)	Suganthi and Madheswaran (2010)	(b)
Huang et al. (2009a)	(b)	Sulaiman et al. (2012)	(b)
Huang et al. (2009b)	(a) (b)	Tahmasbi et al. (2011)	(b)
Álvarez Illán et al. (2010)	(b)	Tan et al. (2010)	(a) (b)
Itai et al. (2009)	(b)	Tanner et al. (2006)	(b)
Jasmine et al. (2009)	(b)	Tolouee et al. (2011)	(b)
Korfiatis et al. (2007)	(b)	Usha and Sandya (2013)	(b)
Korotkov and Garcia (2012)	(c)	Verikas et al. (2006)	(b)
Kovacs et al. (2006)	(a) (b)	Verma (2009)	(b)
Kuang and Ye (2008)	(b)	Vertan et al. (2011)	(b)
Kumar et al. (2011)	(a) (b)	Voigt et al. (2010)	(b)
Lartizien et al. (2014)	(a) (b)	Volpi et al. (2009)	(b)
Lee et al. (2009)	(a) (b)	Wada et al. (2006)	(b)
Lerdsinmongkol et al. (2011)	(a) (b)	Wang et al. (2009)	(b)
Li et al. (2009)	(a) (b)	Wittenberg et al. (2012)	(b)
Li et al. (2012)	(a) (b)	Wu et al. (2006)	(b)
Liu et al. (2012)	(a) (b)	Xiao et al. (2010)	(b)
Liu et al. (2013)	(b)	Zhang et al. (2011)	(a) (c)
López et al. (2008)	(b)	Zheng et al. (2008)	(a) (b)

Rev. Bras. Eng. Bioméd., v. 30, n. 4, p. 355-383, dez. 2014
Braz. J. Biom. Eng., 30(4), 355-383, Dec. 2014

Table 3. Journals that provided the included papers.

Journals
Academic Radiology (ISSN: 1076-6332)
ACM Journal of Data and Information Quality (ISSN: 1936-1955)
Artificial Intelligence in Medicine (ISSN: 0933-3657)
Australasian Physical & Engineering Sciences in Medicine (ISSN: 0158-9938)
Biomedical Engineering/Biomedizinische Technik (ISSN: 1862-278X)
Biomedical Signal Processing and Control (ISSN: 1746-8094)
Clinical Neurology and Neurosurgery (ISSN: 0303-8467)
Computers in Biology and Medicine (ISSN: 0010-4825)
Electronics Letters (ISSN: 0013-5194)
EURASIP Journal on Advances in Signal Processing (ISSN: 1687-6180)
Expert Systems (ISSN: 1468-0394)
Expert Systems with Applications (ISSN: 0957-4174)
IEEE Journal of Biomedical and Health Informatics (ISSN: 2168-2194)
IEEE Journal of Selected Topics in Signal Processing (ISSN: 1932-4553)
IEEE Transactions on Information Technology in Biomedicine (ISSN: 1089-7771)
IEEE Transactions on Nuclear Science (ISSN: 0018-9499)
International Journal of Computer Assisted Radiology and Surgery (ISSN: 1861-6410)
Investigative Ophthalmology & Visual Science (ISSN: 0146-0404)
Journal of Gastroenterology and Hepatology (ISSN: 1440-1746)
Machine Vision and Applications (ISSN: 0932-8092)
Magnetic Resonance in Medicine (ISSN: 1522-2594)
Medical & Biological Engineering & Computing (ISSN: 0140-0118)
Medical Image Analysis (ISSN: 1361-8415)
Medical Physics (ISSN: 0094-2405)
Neurocomputing (ISSN: 0925-2312)
Neuroscience Letters (ISSN: 0304-3940)
Nuclear Medicine Communications (ISSN: 0143-3636)
Osteoporosis International (ISSN: 0937-941X)
Pattern Recognition Letters (ISSN: 0167-8655)
Radiology (ISSN: 0033-8419)
Skin Research and Technology (ISSN: 1600-0846)
Turkish Journal of Electrical Engineering & Computer Sciences (ISSN: 1300-0632)
Ultrasound in Medicine & Biology (ISSN: 0301-5629)
World Journal of Gastroenterology (ISSN: 1007-9327)

Table 4. Collections that provided the included papers.

Collections
Advances in Neuro-Information Processing (Lecture Notes in Computer Science, ISBN: 978-3-642-02489-4)
Advances in Visual Computing - Part II (Lecture Notes in Computer Science, ISBN: 978-3-540-48626-8)
Computer Analysis of Images and Patterns (Lecture Notes in Computer Science, ISBN: 978-3-540-74271-5)
Digital Mammography (Lecture Notes in Computer Science, ISBN: 978-3-540-35625-7)
Image Analysis and Recognition (Lecture Notes in Computer Science, ISBN: 978-3-540-44894-5)
Knowledge-Based Intelligent Information and Engineering Systems (Lecture Notes in Computer Science, ISBN: 978-3-540-74828-1)
Medical Biometrics (Lecture Notes in Computer Science, ISBN: 978-3-642-13922-2)
Medical Image Computing and Computer-Assisted Intervention - MICCAI 2009 (Lecture Notes in Computer Science, ISBN: 978-3-642-04270-6)
Medical Imaging and Augmented Reality (Lecture Notes in Computer Science, ISBN: 978-3-540-37220-2)
Progress in Pattern Recognition, Image Analysis and Applications (Lecture Notes in Computer Science, ISBN: 978-3-540-85919-2)

Table 5. Proceedings that provided the included papers.

Proceedings
Annual ACM Bangalore Conference
Annual IEEE India Conference
Annual International Conference of the IEEE Engineering in Medicine and Biology Society
Biomedical Engineering International Conference
Congress on Image and Signal Processing
E-Health and Bioengineering Conference
IEEE International Conference on Control System, Computing and Engineering
IEEE International Conference on Robotics and Biomimetics
IEEE International Conference on Signal Processing and Communications
IEEE International Symposium on Biomedical Imaging
IEEE International Workshop on Imaging Systems and Techniques
International Conference and Workshop on Emerging Trends in Technology
International Conference on Advances in Computing, Communications and Informatics
International Conference on Biomedical Engineering and Informatics
International Conference on Computer Information Science
International Conference on Computing: Theory and Applications
International Conference on Control, Automation, Communication and Energy Conservation
International Conference on Emerging Trends in Electrical Engineering and Energy Management
International Conference on Natural Computation
International Conference on Signal Processing
International Conference on Signal Processing, Communication, Computing and Networking Technologies
International Conference on Signal Processing, Communications and Networking
International Joint Conference on Neural Networks
International Symposium on Applied Sciences in Biomedical and Communication Technologies
International Symposium on Computer-Based Medical Systems
International Symposium on Intelligent Information Technology Application
International Symposium on Signals, Circuits and Systems
Iranian Conference of Biomedical Engineering
National Radio Science Conference
SPIE Medical Imaging: Computer-Aided Diagnosis
SPIE Medical Imaging: Image Perception, Observer Performance and Technology Assessment

sources from which studies included in this SR were taken. The next section presents and discusses the results obtained through this SR.

Results and Discussion

Table 6 presents the 98 CAD systems reported in the 96 included studies (Pietka et al. (2010) reported the development of three distinct systems). In the following subsections, an overview of the state of the art regarding the development and assessment of CAD systems is presented based on the studies included through the SR.

Abnormalities studied

As seen in Table 6, there is a significant variety of abnormalities that are currently subjects of study for the development of CAD systems. As shown in Figure 2, breast cancer and lung cancer are the diseases most commonly studied within the scope of this SR. Such evidence is significant, considering the importance of early diagnoses of many different types of neoplasia is well known.

In addition to the diseases mentioned, other abnormalities were also reported, encompassing the processing of medical images of different structures and organs of the human body, including brain, skin, retina, bones, heart, arteries, liver, ear, prostate, and gastrointestinal tract, among others (Table 6). CAD systems are the subject of study and research with applicability in a wide range of various medical areas. Although many approaches are still far from clinical application, the variety of ideas, techniques and application areas show that one can expect significant development in computational applications for the diagnosis of many well-known abnormalities.

Modalities of medical imaging exploited

Different types of medical imaging have been objects of study for the development of CAD systems. This statement is confirmed by observing the results of this SR. From the 29 systems that reported dealing

Rev. Bras. Eng. Bioméd., v. 30, n. 4, p. 355-383, dez. 2014
Braz. J. Biom. Eng., 30(4), 355-383, Dec. 2014

Table 6. CAD systems presented in the included papers of the SR.

Reference	Disease	Imaging modality	Interest	Evaluation methods
Kovacs et al. (2006)	Acute aortic dissection	Computed Tomography	Segmentation of the Aortic Dissection Membrane	Average distance between automatic segmentation and ground truth
Chan (2010)	Acute intracranial hemorrhage	Computed Tomography	Detection	FP rate per case and per image, ROC (and area under the ROC curve), sensitivity
Charbonnier et al. (2013)	Acute ischemic stroke	Computed Tomography Angiography	Detection of hypoperfused brain areas	Positive predictive value, ROC (and area under the ROC curve), sensitivity
Chang et al. (2006)	Acute ischemic stroke	Magnetic Resonance	ROIs segmentation	Volume (mm3). Comparison with other approaches. Ground truth based on manual calculation of size and volume. Performance based on execution time and application usability.
Álvarez Illán et al. (2010)	Alzheimer's disease	Computed Tomography	Classification	Correct classification rate (accuracy), sensitivity, specificity
Ramírez et al. (2009)	Alzheimer's disease	Computed Tomography	Detection	Correct detection rate (accuracy), sensitivity, specificity
López et al. (2011)	Alzheimer's disease	Computed Tomography	Detection	Correct detection rate (accuracy), positive and negative likelihood rate, ROC (and area under the ROC curve), sensitivity, specificity
Segovia et al. (2012)	Alzheimer's disease	Computed Tomography	Detection	Negative likelihood, positive likelihood, ROC, sensitivity, specificity
Grana et al. (2011)	Alzheimer's disease	Magnetic Resonance	Detection	Correct detection rate (accuracy), sensitivity, specificity
Huang et al. (2007)	Bone lesions	Bone Scintigraphy	Lesion detection	Number of FP per case, sensitivity
Huang et al. (2009a)	Bone lesions	Computed Tomography	Lesion detection	Correct detection rate (accuracy), number of FP, number of FN
Sato et al. (2011)	Brain atrophy	Magnetic Resonance	Segmentation of brain tissues	F-value, Overlap
Xiao et al. (2010)	Brain pathologies	Computed Tomography	Detection	ROC (and area under the ROC curve), sensitivity, specificity
Wittenberg et al. (2012)	Breast cancer	Digital Tomosynthesis	Lesion segmentation	Over-segmentation, under-segmentation
Tanner et al. (2006)	Breast cancer	Magnetic Resonance	Lesion classification	ROC (and area under the ROC curve)
Retter et al. (2013)	Breast cancer	Magnetic Resonance	Lesions classification	ROC (and area under the ROC curve)
Bhooshan et al. (2011)	Breast cancer	Magnetic Resonance	Classification (probability of malignancy)	P-value, ROC (and area under the ROC curve)
Tahmasbi et al. (2011)	Breast cancer	Mammography	Classification	FN Rate, FP rate, ROC (and area under the ROC curve)
Wu et al. (2006)	Breast cancer	Mammography	Classification	FP rate, FROC curve, sensitivity
López et al. (2008)	Breast cancer	Mammography	Classification	TP rate, positive predictive value
Muramatsu et al. (2013)	Breast cancer	Mammography	Classification	ROC (and area under the ROC curve)
Wang et al. (2009)	Breast cancer	Mammography	Detection	ROC (and area under the ROC curve)

Table 6. Continued...

Reference	Disease	Imaging modality	Interest	Evaluation methods
Ramos et al. (2012)	Breast cancer	Mammography	Lesion detection	ROC (and area under the ROC curve)
Song et al. (2010)	Breast cancer	Mammography	Lesion segmentation	Difference between edges based in distances, Overlap, over-segmentation, under-segmentation
Geetha et al. (2008)	Breast cancer	Mammography	Microcalcification classification	ROC, sensitivity, specificity
Jasmine et al. (2009)	Breast cancer	Mammography	Microcalcification classification	Sensitivity
Osman et al. (2009)	Breast cancer	Mammography	Microcalcification classification	Sensitivity, specificity
Giannakopoulou et al. (2010)	Breast cancer	Mammography	Microcalcification classification	ROC (and area under the ROC curve), sensitivity, specificity
García-Orellana et al. (2008)	Breast cancer	Mammography	Microcalcification detection	FROC, sensitivity
Gedik and Atasoy (2013)	Breast cancer	Mammography	ROIs classification	Correct classification rate (accuracy), ROC, sensitivity, specificity
Verma (2009)	Breast cancer	Mammography	ROIs classification	Correct classification rate (accuracy)
Haindl et al. (2007)	Breast cancer	Mammography	ROIs segmentation	Indexes of the Prague Texture Segmentation Datagenerator and Benchmark (Haindl and Mikes, 2008)
Zheng et al. (2008)	Breast cancer	Mammography	ROIs segmentation and classification	Segmentation: relative area difference; Classification: ROC (and area under the ROC curve)
He et al. (2011)	Breast cancer	Mammography	Segmentation of tissue structure and risk classification	Segmentation: comparison between automated and manual segmentation; Risk classification: satisfaction of health professionals, sensitivity
Suganthi and Madheswaran (2010)	Breast cancer	Mammography	Tumor classification	Correct classification rate (accuracy), ROC (and area under the ROC curve)
Filipczuk et al. (2013)	Breast cancer	Microscopic/ Cytologic Images	Classification	Classification: correct classification rate (accuracy), Matthews correlation coefficient, sensitivity, specificity
Markkongkeaw et al. (2013)	Breast cancer	Microscopic/ Cytologic Images (breast tissue cells)	Classification of histological structures	Correct classification rate (accuracy)
Lee et al. (2009)	Breast cancer	Ultrasonography	Lesion classification	Correct classification rate (accuracy), Fisher estimator, negative predictive value, precision, ROC (and area under the ROC curve), sensitivity, specificity
Gruszauskas et al. (2008)	Breast cancer	Ultrasonography	Lesion classification	Segmentation: Overlap; Classification: ROC (and area under the ROC curve)

Rev. Bras. Eng. Bioméd., v. 30, n. 4, p. 355-383, dez. 2014
Braz. J. Biom. Eng., 30(4), 355-383, Dec. 2014

Table 6. Continued...

Reference	Disease	Imaging modality	Interest	Evaluation methods
Shen et al. (2007)	Breast cancer	Ultrasonography	Lesion classification	Level of agreement between the results of the radiologists and the system: Kappa's statistics; Classification: correct classification rate (accuracy), negative predictive value, precision, ROC (and area under the ROC curve), sensitivity, specificity
Gruszauskas et al. (2009)	Breast cancer	Ultrasonography	Lesion classification	ROC (and area under the ROC curve)
Moon et al. (2011)	Breast cancer	Ultrasonography	Nodule classification	Correct classification rate (accuracy), negative predictive value, positive predictive value, P-value, ROC (and area under the ROC curve), sensitivity, specificity
Shilaskar and Ghatol (2013)	Cardiovascular diseases	Computed Tomography	Detection	Correct detection rate (accuracy), sensitivity, specificity
Liu et al. (2012)	Cardiovascular diseases	Magnetic Resonance	Segmentation of left ventricle	Average perpendicular distance, Dice's coefficient, Left Ventricle ejection fraction, Left Ventricle mass, percentage of good contours
Sulaiman et al. (2012)	Cervical cancer	Microscopic/ Cytologic Images (cervical cells)	Lesion classification	Correct classification rate (accuracy), sensitivity, specificity
Nava et al. (2014)	Chronic obstructive pulmonary disease (emphysema)	Computed Tomography	Emphysema classification	Correct classification rate (accuracy)
Bevilacqua (2013)	Colon and rectal cancers	Computed Tomography Colonography	Polyps detection	Correct detection rate (accuracy), FP rate, sensitivity, specificity
Kuang and Ye (2008)	Dental caries	Radiography	Detection of caries	Sensitivity
David et al. (2008)	Diabetic retinopathy	Retinography	Classification	Correct classification rate (accuracy)
Hatanaka et al. (2011)	Diabetic retinopathy	Retinography	Hemorrhage detection	sensitivity, specificity
Sanchez et al. (2011)	Diabetic retinopathy	Retinography	Lesion detection	ROC (and area under the ROC curve), sensitivity, specificity
Voigt et al. (2010)	Functional voice disorders	Endoscopy and Phonovibrograms	Frequency classification of vocal fold movements	Correct classification rate (accuracy)
Miyaki et al. (2013)	Gastric cancer	Endoscopy	Detection	Correct detection rate (accuracy), ROC, sensitivity, specificity
Tan et al. (2010)	Glaucoma	Retinography	Segmentation of optic cup	Area overlap error (1 - Overlap), relative area difference
Tolouee et al. (2011)	Interstitial lung diseases	Computed Tomography	Classification of lung tissue patterns	Confusion matrix, correct classification rate (accuracy), Kappa's statistic, sensitivity, specificity
Raja et al. (2007)	Kidney disorders	Ultrasonography	Classification of kidney disorders	Correct classification rate (accuracy)

Table 6. Continued...

Reference	Disease	Imaging modality	Interest	Evaluation methods
Kumar et al. (2011)	Liver cancer	Computed Tomography	Tumor detection	Correct detection rate (accuracy), negative predictive value, positive predictive value, sensitivity, specificity
Streba et al. (2012)	Liver cancer	Ultrasonography	Classification of several types of liver cancer	Correct classification rate (accuracy), negative predictive value, positive predictive value, sensitivity, specificity
Korfiatis et al. (2007)	Lung cancer	Computed Tomography	Lung Segmentation	Segmentation: Overlap; Correctness of the segmented edge: average, difference in the shape of the segmented edge, maximum distance between segmented volumes, root mean square
Volpi et al. (2009)	Lung cancer	Computed Tomography	Mediastinum segmentation	Rate of carcinogenic areas extracted correctly (accuracy)
Gomathi and Thangaraj (2010)	Lung cancer	Computed Tomography	Nodule detection	Number of FP per case, number of TP detected by CAD versus number of TP detected by specialist, sensitivity
Itai et al. (2009)	Lung cancer	Computed Tomography	Nodule detection	Number of FP per case, sensitivity
Ashwin et al. (2012)	Lung cancer	Computed Tomography	Nodule detection	Detection (network performance): confusion matrix, correct detection rate (accuracy), FP rate, mean square error, regression analysis, ROC (and area under the ROC curve), sensitivity, specificity
Wada et al. (2006)	Lung cancer	Computed Tomography	Nodule detection	Number of FP per slice, positive predictive value
Pietka et al. (2010) (a)	Lung cancer	Computed Tomography	Nodule detection	FP rate, sensitivity
Endo et al. (2012)	Lung cancer	Computed Tomography	Nodule segmentation and classification	Segmentation: Dice's coefficient; Classification: Correct classification rate (accuracy)
Elizabeth et al. (2012)	Lung cancer	Computed Tomography	Lung segmentation	Correct region detection rate (accuracy), precision, sensitivity (recall), specificity
Nagata et al. (2013)	Lung cancer	Radiography	Nodule detection	FROC curve, number of FP per image, sensitivity
Al-Absi et al. (2012)	Lung cancer	Radiography	Nodule detection	Correct detection rate (accuracy), FN rate, FP rate
Schilham et al. (2006)	Lung cancer	Radiography	Nodule detection	Segmentation: Overlap; Detection: FROC
Sasaki et al. (2010)	Lung cancer and other lung abnormalities	Radiography	Abnormalities detection	FN rate (FRR - False Rejection Rate), FP rate (FAR -False Acceptance Rate)
Lartizien et al. (2014)	Lynphoma	Computed Tomography	Classification	ROC (and area under the ROC curve), TOP10 method
Pietka et al. (2010) (b)	Multiple sclerosis	Magnetic Resonance	Detection of brain lesions	Sensitivity, specificity, similarity

Rev. Bras. Eng. Bioméd., v. 30, n. 4, p. 355-383, dez. 2014
Braz. J. Biom. Eng., 30(4), 355-383, Dec. 2014

Table 6. Continued...

Reference	Disease	Imaging modality	Interest	Evaluation methods
Huang et al. (2009b)	Nuclear cataract	Slit lamp	Classification	Ranking of cases: normalized discounted cumulative gain; Classification: accuracy in the prediction of score to images, mean error between predicted scores and scores defined by experts
Muramatsu et al. (2013)	Osteoporosis	Radiography	Detection of osteoporotic risk	Sensitivity, specificity
Roberts et al. (2010)	Osteoporosis	Radiography	Detection of vertebral fractures	FP rate, ROC, sensitivity
Vertan et al. (2011)	Otitis	Otoscopy	Otitis detection	Correct detection rate (accuracy)
Mironică et al. (2011)	Otitis	Otoscopy	Otitis detection	Correct detection rate (accuracy)
Usha and Sandya (2013)	Ovarian abnormalities	Ultrasonography	Segmentation, measurement and feature extraction of ovarian	Percentage of error in the measurements (based on measurements made manually by experts)
Martinez-Murcia et al. (2014)	Parkinson	Computed Tomography	Detection	Correct detection rate (accuracy), negative likelihood, positive likelihood, sensitivity, specificity
Hebert et al. (2012)	Pathological state of pulmonary alveoli	Confocal Microscopy	Classification	Correct classification rate (accuracy)
Lerdsinmongkol et al. (2011)	Pleural mesotelioma	Computed Tomography	Pleura segmentation	Bit quads, 3D connected component labeling
Pietka et al. (2010) (c)	Pneumothorax	Computed Tomography	Segmentation	Sensitivity, specificity
Ampeliotis et al. (2007)	Prostate cancer	Magnetic Resonance	Classification of prostate tissues	Correct classification rate (accuracy)
Liu et al. (2013)	Prostate cancer	Magnetic Resonance	Detection	ROC (and area under the ROC curve)
Mumcuoglu et al. (2011)	Renal cortical scars	Renal Cortical Scintigraphy	Detection of cortical scars	FROC
Raja et al. (2010)	Renal cysts	Ultrasonography	Classification of cases	Cross validation with specialist analysis results, F-score, ROC
Cheng et al. (2012)	Retinal diseases	Retinography	Segmentation of optic disk	Area overlap error (1 - Overlap)
Garnavi et al. (2011)	Skin cancer	Dermatoscopy	Detection of melanoma edges	Correct detection rate (accuracy), edge error, positive predictive value, sensitivity, similarity, specificity
Barhoumi et al. (2007)	Skin cancer	Dermatoscopy	Lesion classification	Correct classification rate (accuracy), precision versus revocation, ROC
Beuren et al. (2012)	Skin cancer	Dermatoscopy	Lesion segmentation	correct pixel classification rate (accuracy), error, F-measure, misclassification error, negative rate metric, precision, relative area difference, sensitivity (recall), Number of TP-TN-FP-FN
Garnavi et al. (2012)	Skin cancer	Dermatoscopy	Melanoma classification	Correct classification rate (accuracy), ROC (and area under the ROC curve)

Table 6. Continued...

Reference	Disease	Imaging modality	Interest	Evaluation methods
Odeh et al. (2006)	Skin cancer	Fluorescence Spectroscopy	Lesion classification	Correct classification rate (accuracy), sensitivity, specificity
Li et al. (2012)	Subarachnoid hemorrhage	Computed Tomography	Segmentation of subarachnoid space and Hemorrhage detection	Segmentation: Dice's index, Overlap (relative overlap), spatial overlap; Detection: sensitivity, specificity
Gopinath and Shanthi (2013)	Thyroid cancer	Microscopic/ Cytologic Images	Classification	Correct classification rate (accuracy), sensitivity, specificity
Charisis et al. (2013)	Ulcer	Endoscopy	Detection of ulcer regions	Correct detection rate (accuracy), sensitivity, specificity
Li et al. (2009)	Ulcer	Wireless Capsule Endoscopy	Detection of small bowel ulcer	Correct detection rate (accuracy), sensitivity, specificity
Verikas et al. (2006)	Vocal cord diseases	Vocal Cord Images	Classification	Correct classification rate (accuracy)

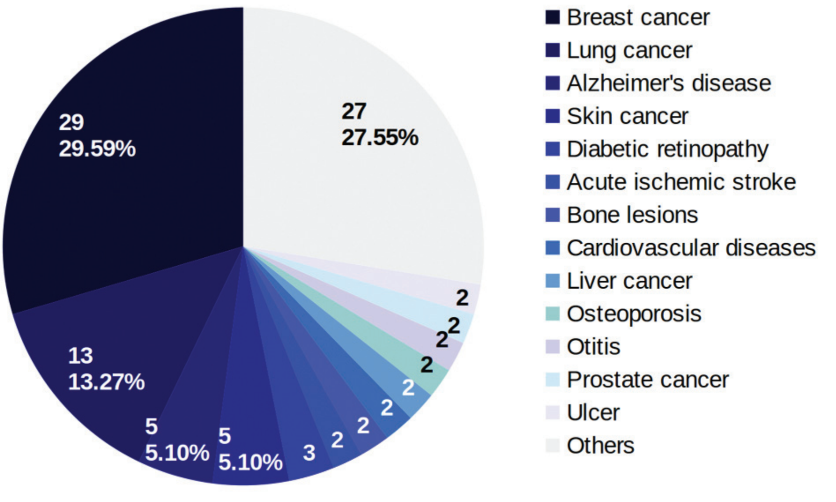

Figure 2. Number of CAD systems used for each abnormality.

with breast cancer, eighteen (62.07%) addressed mammograms. Mammography is the most effective technique for the early diagnosis of breast cancer (Giger, 1999). Thus, the utilization of such images is still very important due to the possibility that a physician may misread or misinterpret an exam (Giannakopoulou et al. 2010; Jasmine et al. 2009; Osman et al. 2009; Verma, 2009). Five other systems (17.24%) reported work with ultrasound imaging, a technique that has been very important, in conjunction with mammography, in increasing the precision of breast cancer diagnosis (Giger, 1999; Lee et al., 2009; Shen et al., 2007). Other reported imaging modalities dealing with breast cancer included magnetic resonance imaging (10.34%), microscopic/cytologic imaging (6.90%) and digital tomosynthesis (3.45%). Works with magnetic resonance, microscopic/cytologic imaging and digital tomosynthesis have only been recently developed, which suggests the use of new imaging techniques to aid in breast cancer diagnoses.

The literature search also yielded thirteen CAD systems focused on lung cancer, nine of which (69.23%) used images from CT examinations. The other four systems (30.77%) used chest radiography images.

Five systems reported in this review addressed the diagnosis of Alzheimer's disease. Four (80%) used CT images, while only one report used magnetic resonance images.

Rev. Bras. Eng. Bioméd., v. 30, n. 4, p. 355-383, dez. 2014
Braz. J. Biom. Eng., 30(4), 355-383, Dec. 2014

Four systems reported using images from dermatoscopy examinations to address skin cancer, while only one used images from fluorescence spectroscopy.

Five systems were reported to diagnose eye diseases affecting the retina using processed retinography images. In turn, the system used to diagnose nuclear cataracts (Huang et al., 2009b) worked with images obtained by means of a slit lamp.

The graph in Figure 3 presents the number of systems for each medical imaging method in the studies. In this graph, each reported system is evaluated for modality, independent of the studied abnormality. As seen, images from CTs and mammographies were the most exploited for the development of CAD systems.

Tasks for computer-aided diagnosis systems

Each developed technique performed a specific task utilizing a computer-aided diagnosis. In general, a complete CAD system involved segmented structures, the detection of abnormalities and the extraction of their characteristics for a subsequent classification of the problem (e.g., normal, benign or malignant, depending on the case). For example, to classify structures, the previous stages of segmentation and detection are required. Studies with CAD schemes have contributed to the automation of these tasks, either by means of developing a new technique or improving an existing technique. For each task of interest, the charts presented in Figure 4, Figure 5 and Figure 6 show the number of reported systems that contributed innovations.

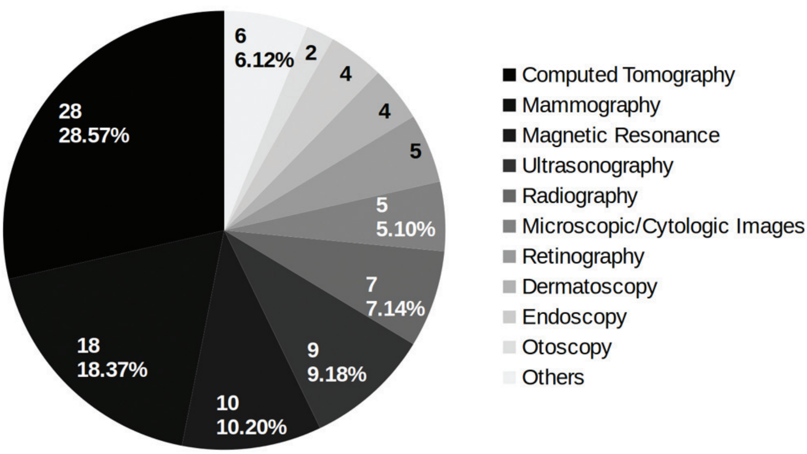

Figure 3. Number of CAD systems used for each medical imaging modality.

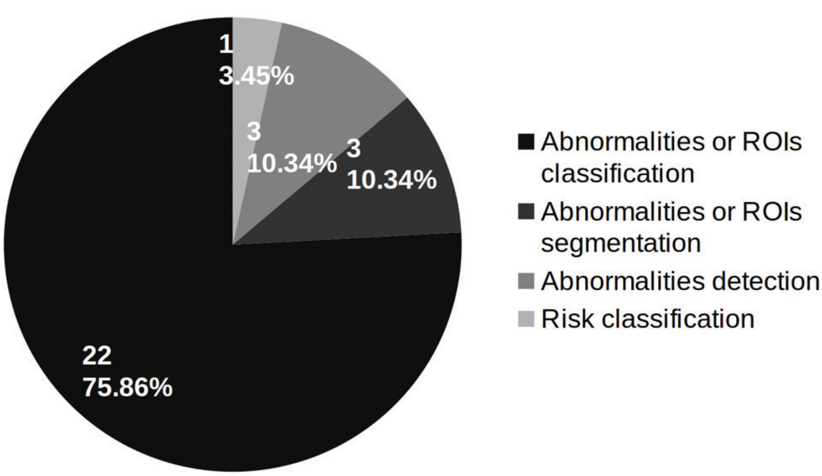

Figure 4. Tasks executed in the CAD systems: tasks of CAD systems for breast cancer.

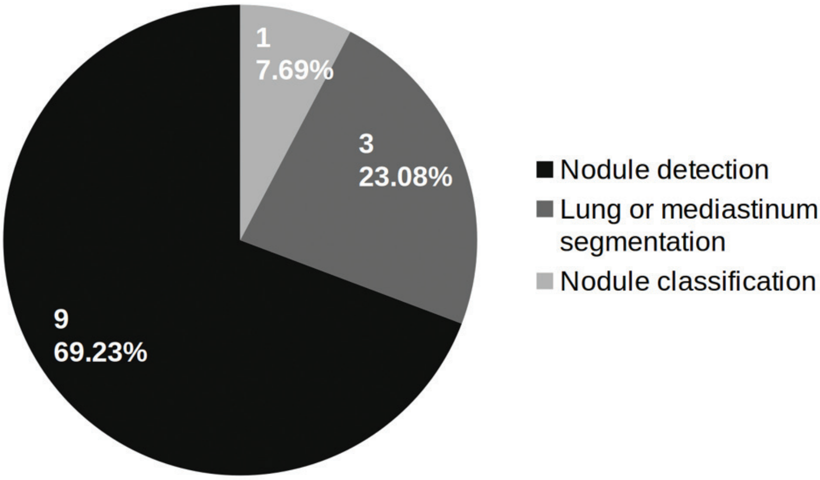

Figure 5. Tasks executed in the CAD systems: tasks of CAD systems for lung cancer.

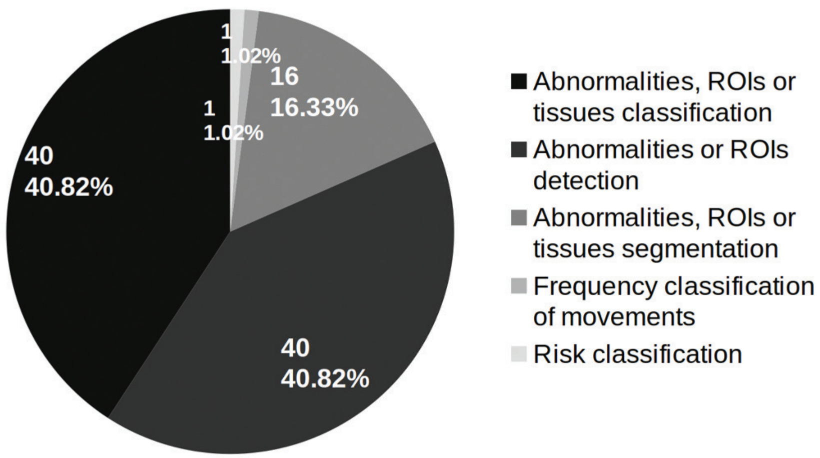

Figure 6. Tasks executed in the CAD systems: tasks of all reported systems.

Most of the CAD systems used for the diagnosis of breast cancer (Figure 4) aimed at classifying microcalcifications, lesions or other regions of interest (ROIs). This indicates that the main focus of CAD technology for breast cancer is the identification of suspicious structures in medical images and the determination of whether these structures are benign or malignant (i.e., capable of being cancerous). This can help physicians diagnose the disease and its severity level, thereby reducing chances of misinterpretation and aiding in determining recommended treatments.

He et al. (2011) presented an approach to risk classifications for breast cancer, i.e., a formula to determine the risk of developing the disease. This risk was estimated by analyzing mammary tissue patterns through mammography.

For lung cancer CAD systems (Figure 5), most systems were designed to detect nodules. Regardless of the disease studied, it can be seen that the main tasks of interest were the detection and classification of abnormalities (Figure 6). This was expected because these are the tasks that most reflect the contribution of CAD systems.

Among the reported systems in the reviewed studies, different techniques have been proposed to complete the different aforementioned tasks. Systems utilizing segmentation used techniques based on thresholding (Ashwin et al., 2012; Korfiatis et al., 2007; Liu et al., 2012; Pietka et al., 2010; Suganthi and Madheswaran, 2010; Usha and Sandya, 2013), morphological operators (Beuren et al., 2012; Lerdsinmongkol et al., 2011; Li et al., 2012; Usha and Sandya, 2013; Volpi et al., 2009), fuzzy k-means clustering (Beuren et al., 2012; Li et al., 2012; Wittenberg et al., 2012), region growing (Wittenberg et al., 2012; Zheng et al., 2008), and

Rev. Bras. Eng. Bioméd., v. 30, n. 4, p. 355-383, dez. 2014
Braz. J. Biom. Eng., 30(4), 355-383, Dec. 2014

Gaussian mixture models (Haindl et al., 2007; Tan et al., 2010), among others.

For systems focused on detecting abnormalities, images were analyzed by using techniques to segment structures in the images. A few of the segmentation techniques were based on the Fuzzy Set Theory (Huang et al., 2007; Pietka et al., 2010), thresholding (Garnavi et al., 2011; Gomathi and Thangaraj, 2010) and models (Mumcuoglu et al., 2011; Schilham et al., 2006). Detection approaches were based on the use of classifiers, such as artificial neural networks (Ashwin et al., 2012; Bevilacqua, 2013; García-Orellana et al., 2008; Itai et al., 2009; Kumar et al., 2011; Li et al., 2009; López et al., 2011; Mironică et al., 2011; Sasaki et al., 2010), k-nearest neighbor (Al-Absi et al., 2012; Li et al., 2009; Mironică et al., 2011; Sanchez et al., 2011; Schilham et al., 2006), support vectors machine (Grana et al., 2011; Li et al., 2009; Martinez-Murcia et al., 2014; Mironică et al., 2011; Miyaki et al., 2013; Segovia et al., 2012; Shilaskar and Ghatol, 2013; Wang et al., 2009) and probabilistic classifiers (Li et al., 2012; Liu et al., 2013; Mironică et al., 2011; Ramírez et al., 2009; Vertan et al., 2011).

Finally, for classification tasks, we observed the use of classifiers such as k-nearest neighbor (Filipczuk et al., 2013; Gedik and Atasoy, 2013; Gopinath and Shanthi, 2013; He et al., 2011; Muramatsu et al., 2013; Nava et al., 2014; Odeh et al., 2006; Osman et al., 2009; Raja et al., 2010; Verikas et al., 2006), artificial neural networks (Barhoumi et al., 2007; Geetha et al., 2008; Jasmine et al., 2009; López et al., 2008; Raja et al., 2007; Streba et al., 2012; Verma, 2009; Wu et al., 2006), Bayesian classifiers (Ampeliotis et al., 2007; Bhooshan et al., 2011; Garnavi et al., 2012; Gruszauskas et al., 2008, 2009; Retter et al., 2013; Tolouee et al., 2011) techniques based on linear discriminant analysis (Lee et al., 2009; Muramatsu et al., 2013; Tanner et al., 2006) and logistic regression models (Shen et al., 2007; Tanner et al., 2006).

A few studies combined clustering algorithms with classification algorithms. He et al. (2011) and Raja et al. (2010) both used the k-means and k-nearest neighbor algorithms. Verma (2009) used a clustering algorithm with artificial neural networks trained with back propagation. Barhoumi et al. (2007) classified skin lesions by combining results from artificial neural networks with results of a content-based image retrieval (CBIR) scheme through the Dempster-Shafer Theory.

Public databases of medical images

One of the difficulties encountered in the development of CAD systems is the lack of availability of test cases. It is not always possible to obtain a medical image database containing various acquisition characteristics, structures or abnormalities that a technique requires for the detection, analysis or diagnosis of a disease. Factors such as partnerships with clinics and hospitals, ethical issues, and image access permissions, tend to hamper the task.

For this reason, a few projects have been developed and maintained aiming to provide medical images for research groups that develop CAD technologies. These projects consist of public databases of medical images that document reports made by physicians and often include information about structures of interest in the images.

We cataloged various public databases from the systems reported in the studies.

Digital Database for Screening Mammography - DDSM (García-Orellana et al., 2008; Haindl et al., 2007; Muramatsu et al., 2013; Ramos et al., 2012; Song et al., 2010; Suganthi and Madheswaran, 2010; Verma, 2009; Wang et al., 2009; Zheng et al., 2008): maintained by the University of South Florida, this database serves as a resource for research in mammographic imaging analysis (Heath et al., 2001). The database contains 2,620 cases divided into 43 volumes, each composed of normal cases, cases containing suspicious structures proved benign or proven cases of cancer. Delineations of regions of interest (i.e., ground truth regions), if any, are provided. A set of programs for decoding and manipulating mammography images are also included.

The mini-MIAS database of mammograms (Gedik and Atasoy, 2013; Geetha et al., 2008; He et al., 2011; Jasmine et al., 2009; López et al., 2008; Osman et al., 2009; Tahmasbi et al., 2011; Wu et al., 2006): this database is maintained by the Mammographic Image Analysis Society (MIAS) and offers 322 mammograms for use in research. In addition to mammograms, the database contains information concerning the type, severity and coordinates of the central pixel of abnormalities, if any, in each image (Suckling et al., 1994).

Lung Image Database Consortium - LIDC (Korfiatis et al., 2007; Pietka et al., 2010): this public database is the result of an initiative that aimed to provide chest CT images to support the development, training and assessment of CAD schemes for the detection of pulmonary nodules (Armato III et al., 2011). The database provides exams of 1,010 patients, delimitations of existing lesions, and a software for the manipulation of images.

Japanese Society of Radiological Technology (JSRT) database (Al-Absi et al., 2012; Nagata et al., 2013; Schilham et al., 2006): this database of chest radiographs of the JSRT was created in cooperation with the Japan Radiological Society in 1998. It consists of 247 images, comprising 154 cases of a single pulmonary nodule (grouped by subtlety) and 93 cases without nodules. It also provides information about patients (e.g., age and gender), diagnoses (i.e., benign or malignant) and central coordinates of each node (Shiraishi et al., 2000).

MESSIDOR Digital Retinal Images (Sanchez et al., 2011): the MESSIDOR database was developed to facilitate CAD studies for diabetic retinopathy. It contains 1,200 images of the eye fundus. Moreover, for each image, it provides scores given by experts indicating the level of the retinopathy, and the risk of macular edema (Messidor, 2014).

Digital Retinal Images for Vessel Extraction - DRIVE (Hatanaka et al., 2011; Jiménez et al., 2010): this database was established with the aim of enabling a comparative study on the segmentation of blood vessels in retinal images. To this end, 40 photographs of the retina (eye fundus) are available. For each photo, there are two manually segmented blood vessel images (Staal et al., 2004). Researchers who use the database to test methods for segmentation of blood vessels can submit their results through the home-page of the project, to make them available for comparison with other studies in the area.

STructured Analysis of the Retina - STARE (Jiménez et al., 2010): The STARE project, initiated in 1975 at the University of California, focuses on developing a system to aid in the detection of diseases of the human eye (McCormick and Goldbaum, 1975). The project has a database with 402 eye fundus photographs and a corresponding diagnosis for each image.

Alzheimer's Disease Neuroimaging Initiative - ADNI (López et al., 2011; Segovia et al., 2012): The ADNI (Mueller et al., 2005) has the goal of defining the progression of Alzheimer's disease. To this end, it aims to collect and validate data, such as images from positron emission tomography, magnetic resonance imaging and other sources, to predict the disease. The initiative provides collected data for research purposes. The database contains data and images on 895 patients.

Assessment of CAD systems

As previously mentioned, the main objectives of this SR were to examine and analyze the state of the art of CAD systems. We have already presented the studied abnormalities, medical imaging modalities, tasks of interest and public databases used in the testing and development of the reported systems. In this section, the assessment techniques are discussed.

From Table 6, we see that assessments of CAD systems involved carrying out segmentations, detections or classifications based on a set of inputs and on previously known correct results (provided mostly by specialists) to obtain performance metrics for the system. None of the assessed studies used test criteria established in the literature, such as functional or structural techniques. From this point of view, the assessment is made on an ad hoc basis.

Assessment metrics

Figure 7, Figure 8 and Figure 9 show charts for each diagnosis and the metrics and assessment methods applied to the reported systems. We only considered mentioned methods. However, for the analysis of these

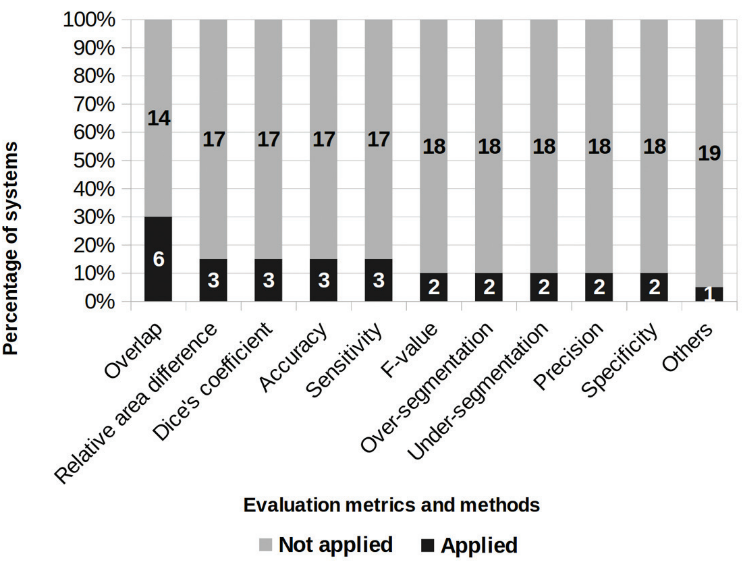

Figure 7. Metrics and methods of assessment used in different tasks to aid diagnosis: segmentation (20 systems reported).

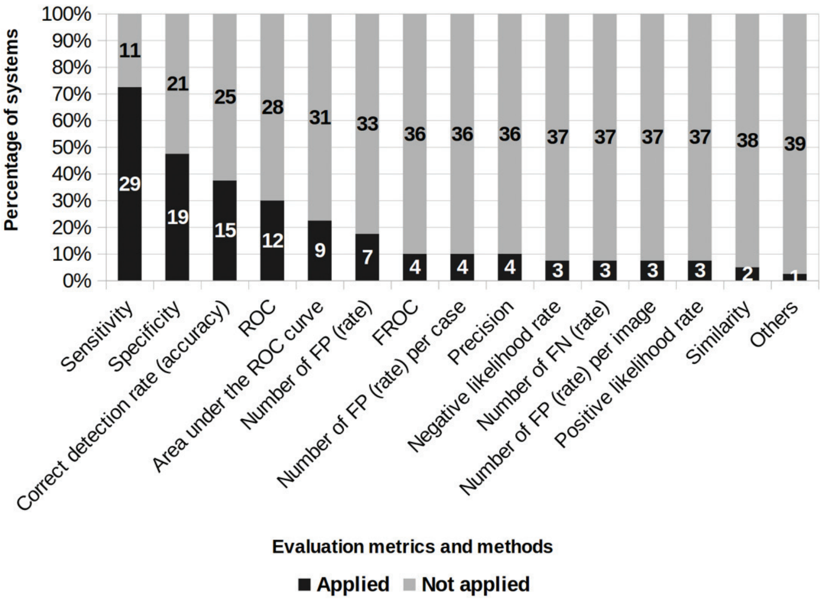

Figure 8. Metrics and methods of assessment used in different tasks to aid diagnosis: detection (40 systems reported).

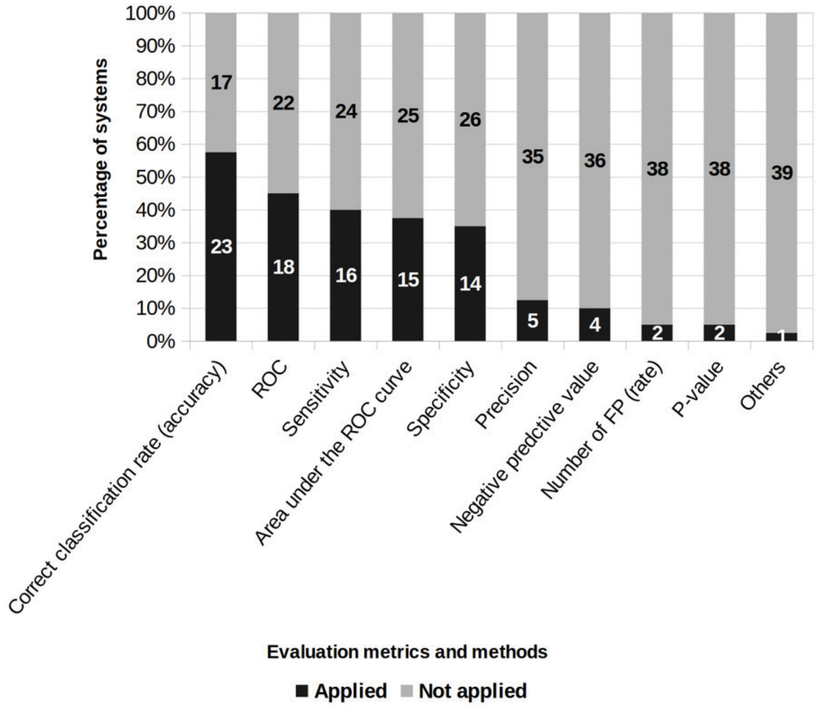

Figure 9. Metrics and methods of assessment used in different tasks to aid diagnosis: classification (40 systems reported).

results, we considered the main tasks of each system and any secondary metrics and methods (Figure 7). For example, if the main task of interest of a given work is the classification of lesions but also reported on the assessment of a previous segmentation task (i.e., mentioning the metrics and/or methods used), these were included in the chart concerning segmentations. For each chart, the total number of reported systems is shown.

The graph in Figure 7 shows that six systems that assessed a segmentation method applied the *overlap* measure. This measurement consisted obtaining the relative area of the intersection between two considered regions (Gruszauskas et al., 2008; Korfiatis et al., 2007) by means of assessing the set of pixels resulting from the segmentation process. Given $|A_{seg}|$, the area of an automatically segmented region A_{seg}, and $|A_{\mathrm{man}}|$, the area of a region A_{man}, which is considered correct for the segmentation process (e.g., generated manually), the overlap measure is defined by Equation 1. A value of 0 indicates the worst performance, i.e., there is no intersection between the correct area and the automatically obtained area. A value of 1 indicates a perfect segmentation.

$$\text{Overlap} = \frac{|A_{\text{seg}} \cap A_{\text{man}}|}{|A_{\text{seg}} \cup A_{\text{man}}|} \quad (1)$$

A relative area difference metric, applied in the assessment of three systems (Beuren et al., 2012; Tan et al., 2010; Zheng et al., 2008), predicts an extension of the automatically segmented region that does not match the expected correct region (Tan et al., 2010). This measure can be obtained through Equation 2. It is seen, that if $A_{seg} = A_{\mathrm{man}}$, then the relative area difference is 0.

$$\text{Relative Area Difference} = \frac{|A_{\text{seg}}| - |A_{\text{man}}|}{|A_{\text{man}}|} \quad (2)$$

A metric applied to evaluate segmentation results, reported in three systems (Endo et al., 2012; Li et al., 2012; Liu et al., 2012), is Dice's coefficient. This metric calculates overlapping areas between an automatically segmented region and the correct expected region (Liu et al., 2012). Equation 3 defines the calculation of this metric. If $|A_{\text{seg}} \cap A_{\text{man}}| = |A_{\text{seg}}| = |A_{\text{man}}|$, then a perfect segmentation results (Dice's coefficient = 1).

$$\text{Dice's coefficient} = \frac{2 \times |A_{\text{seg}} \cap A_{\text{man}}|}{|A_{\text{seg}}| + |A_{\text{man}}|} \quad (3)$$

Other metrics that were also observed for the segmentation assessment included accuracy and sensitivity. These metrics are part of a set of very traditional statistic metrics in the assessment of CAD systems. They are based on true positive (TP), true negative (TN), false positive (FP) and false negative (FN) results (Garnavi et al., 2011), which are concepts defined by Wagner et al. (2007):

- True positive: a positive detection result of an abnormal structure present in the organ or tissue represented in the image, or a correct classification for a detected structure;
- True negative: a negative detection result of an image of an organ or tissue that does not show any abnormal structure, or a correct classification that indicates an abnormal structure that does not belong to a particular class;
- False positive: a positive detection result of an image of an organ or tissue that does not represent any abnormal structure, or an incorrect classification that indicates a particular structure belonging to a given class when, in fact, it does not; and
- False negative: a negative detection result of an image of an organ or tissue that presents one or more abnormal structures that should be detected, or an incorrect classification that indicates a structure that does not belong to a given class when, in fact, it does.

In the case of segmentation, an approach for the use of these metrics is to define TP pixels (i.e., segmented and within the region of interest), TN (outside the region of interest and not segmented), FP (segmented and not within the region of interest) and FN (within the region of interest and not segmented). Later in this section, these metrics are presented in relation to final results of CAD systems. Other methods and assessment metrics, applicable to segmentation routines, were observed in the reported systems are listed in Table 6 and their references.

The metrics and assessment methods applied for the classification and detection tasks are mostly the same. The graphs in Figure 8 and Figure 9 show the metrics and methods used for each particular task, and the chart in Figure 10 show the results for both tasks.

As we can be seen, there was a predominant use of metrics based on TP, TN, FP and FN for the assessment of classification and detection tasks in reported systems. In the combined cases, the sensitivity metric is the most considered method for evaluating a CAD system. Table 7 lists the key reported metrics in Garnavi et al. (2011).

ROC curve

Another widely known method used in the assessment of CAD systems is the Receiver Operating Characteristic (ROC) curve. As seen in Figure 7-10, this method was used to assess 45% of the classification systems reported. Figure 10 combines the applied classification and detection methods and metrics.

This curve represents the sensitivity as a function of the fraction of false positives (FFP = 1 – specificity; Metz, 1999; Wagner et al., 2007). An example of an ROC curve trace is shown in Figure 11. An ideal CAD system presents an operating point (0,1) on the graph, where 0 represents the minimum FFP and 1 represents the maximum sensitivity. The ROC curve estimates operating points that the CAD system can present with variations of specific parameters. For

Rev. Bras. Eng. Bioméd., v. 30, n. 4, p. 355-383, dez. 2014
Braz. J. Biom. Eng., 30(4), 355-383, Dec. 2014

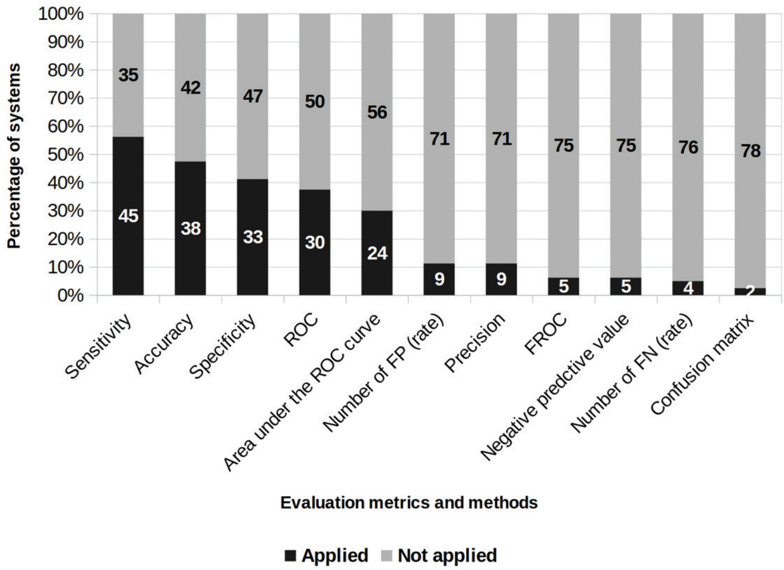

Figure 10. Metrics and methods of assessment used in different tasks to aid diagnosis: classification or detection (80 systems reported).

Table 7. Main metrics and assessment methods reported in the papers.

Metrics	Formula	Description
Sensitivity (or Recall)	$\frac{TP}{TP+FN}(\times 100\%)$	Percentage of abnormalities correctly detected/ classified.
Specificity	$\frac{TN}{TN+FP}(\times 100\%)$	Percentage of normal structures not incorrectly detected/classified as possible abnormalities.
Correct classification / detection rate (Accuracy)	$\frac{TP+TN}{TP+TN+FP+FN}(\times 100\%)$	Percentage of abnormalities and normal structures correctly classified/detected.
Similarity	$\frac{2\times TP}{2\times TP+FN+FP}(\times 100\%)$	Representation of the level of matching between the obtained results and the expected results (taken as true).
Precision (or Positive predictive value)	$\frac{TP}{TP+FP}(\times 100\%)$	Percentage of detected structures that are actually abnormalities.
Negative predictive value	$\frac{TN}{TN+FN}(\times 100\%)$	Percentage of normal structures detected/classified that does not really represent abnormalities.

example, this permits the comparison of performances of multiple techniques, and considers performance changes with parameter variations.

An assessment metric extracted from the ROC curve and often employed in the assessment process of the systems is the *area under the ROC curve*. The larger the area under the curve, the better the performance of the CAD system. More details regarding this metrics can be obtained in Metz (1999) and other included studies.

FROC curve

Another curve used in the assessment of CAD systems is the Free-Response Receiver Operating Characteristic (FROC) curve. This curve represents the sensitivity as a function of the average number of false positives per image (Nishikawa, 2007). Despite having been employed in few reported systems, this method is worth mentioning given the scope of this SR.

To show the differences between an FROC curve and a conventional ROC curve, Metz (1999) used an example of structure detection. A conventional ROC curve provides the probability for a positive region (i.e., containing an abnormal structure) to be diagnosed as positive (sensitivity) and the probability for a negative region (i.e., containing no abnormal structure) to be diagnosed as positive (FFP). An FROC curve provides the probability that a randomly selected lesion will be detected after an average number of FP detections.

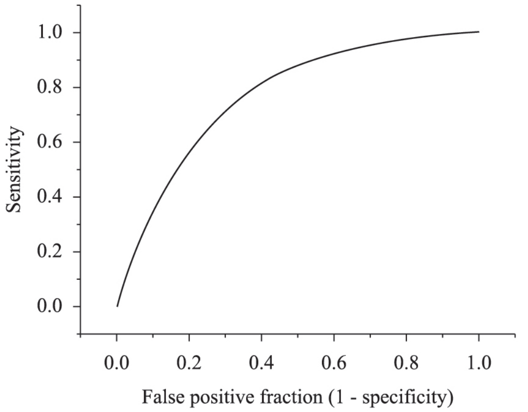

Figure 11. Example of an ROC curve trace.

Metz (1999) also showed that ROC curves are restricted to cases in which there are two detection possibilities for each image or region processed. FROC curves can be used when a lesion may be present in more than one position in each image; the CAD scheme attempts to detect the lesion in all possible locations (Metz, 1999).

Review and theoretical papers

Four review and theoretical papers about CAD systems and trends in the last decade were included in this SR.

Shiraishi et al. (2009) conducted a survey on the use of ROC curves in medical imaging analyses from studies published in Radiology Journal. The researchers analyzed 295 studies published between 1997 and 2006 containing the phrase, "receiver operating characteristic". Approximately 79% of the studies reported findings based on subjective diagnoses or objective measurements, while 14.6% did not include human observers. Most works of the latter evaluated CAD systems.

Pietka et al. (2011) presented and discussed the participation of health professionals and technicians in various stages of the life cycle (i.e., design, assessment and implementation) of CAD systems. The researchers used their own CAD systems to examine how consecutive stages were developed by the multidisciplinary team.

Zhang et al. (2011) presented a review about recent advances in breast tissue classification technologies of CAD systems for breast cancer. The researchers did not present the review methodology; instead, they discussed three classification approaches (texture feature analysis, statistical modeling and machine learning) and compared results obtained from analyzed studies. According to the researchers, machine learning is the most feasible approach to developing universal CAD systems.

Korotkov and Garcia (2012) presented a review about computerized analyses of pigmented skin lesions in microscopic (dermatoscopic) and macroscopic (clinical) images. The researchers presented an extensive background about applied field concepts and described features and methodologies used in the analyzed studies.

Trends and opportunities

From the studies included in this review, the most explored subjects were breast and lung cancers. However, we believe other diseases diagnoses are as important, especially those related to the heart and the brain, which have caused many deaths worldwide. CAD schemes for aiding early disease diagnoses in these areas could potentially improve treatment therapies and thereby effect higher rates of positive outcomes.

Several types of images have been used in the reviewed studies, with X-ray images being the most frequent. However, most CAD systems only considered one type of image, perhaps due to the difficulty in simultaneously evaluating multiple images with diverse formats and characteristics. The evaluation of the combination of different image types may be an interesting subject to explore.

All analyzed studies developed techniques for detecting, segmenting or classifying structures to compose CAD systems. No study proposed any other procedure; all works used traditional approaches to evaluate their results. The limitations of these approaches and the non-standardization of the databases used in evaluations are further discussed in the following section.

Traditional metrics (e.g., ROC and FROC curves) are based on TP, TN, FP and FN results; thus, they depend on prior knowledge of case characteristics used to test CAD systems. For example, to identify actual lesions from medical images, the actual details and characteristics of structures of lesions in an image must be known beforehand. Therefore, there is a chance for normal, benign structures to be mistakenly considered as lesions.

Typically, in this type of evaluation, physician participation is mandatory every time the CAD presents a new technique or approach. The "visual" analyses of each case and the comparison of CAD results against traditional diagnoses must be performed by an experienced medical professional (e.g., a physician or radiologist). Therefore, the testing and evaluation of CAD systems using such metrics is resource-intensive. Whenever any part of the system is modified, subsequent results validation is required. An

Rev. Bras. Eng. Bioméd., v. 30, n. 4, p. 355-383, dez. 2014
Braz. J. Biom. Eng., 30(4), 355-383, Dec. 2014

additional complication is that a physician evaluation can vary, depending on factors such as experience, fatigue, and time availability, as cited by Aziz et al. (2004), Barlow et al. (2004), and Pindborg et al. (1985). Appropriate method for evaluating these systems have yet to be determined and can constitute new opportunities for exploration. Consequently, more reliable systems may be able to decrease variations and improve the quality of diagnoses.

We did not encounter any articles mentioning the use of software engineering techniques, such as software testing, in conjunction with other evaluation approaches. While traditional techniques are not ideal subjects for new publications, it is well known that in specific domains, testing activities require adapted or new techniques. In particular, complexities of input and output domains of image processing software might pose a real challenge for software engineers. Selecting robust test cases from a large, complex and diverse data set is not a trivial task and has not been adequately studied. In addition, using software testing metrics with traditional approaches for CAD evaluations has not yet been explored. However, the present study considers only scientific and academic works; commercial products were out our scope. Thus, we only considered data related to the studied articles.

We suggest and discuss some research approaches within this scope by using Content-Based Image Retrieval (CBIR) concepts to evaluate CAD outputs and test criteria definitions and applications. This permits the identification of errors in the software and computational testing tools. As a result, the CAD evaluation becomes more objective and effective.

In recent years, CBIR techniques have been explored to aid in image retrieval and to assist the physician in composing a diagnosis based on data from similar cases. CBIR systems use features related to color, shape, texture and distance to calculate the similarity between images and their features. We believe concepts from CBIR could be extended to compose more objective approaches to evaluate CAD systems. In the suggested CBIR approach, the expert is required to determine one correct solution (i.e., a model image), and extractors automatically verify whether the answer produced by the image processing program has similar characteristics as that of the model image. Thus, our approach avoids a reliance on potentially biased diagnoses for verification. From a software engineering standpoint, this is an important improvement because testing processes are resource-intensive and are often required during software development and maintenance.

A few standardized databases were used in the reviewed studies. However, none of these databases were complete, i.e., a few databases did not have all structure types, others presented hard-to-process image formats, and still others did not provide enough information for testing techniques. Thus, the creation of image databases to serve as reliable benchmarks, with standardized image formats, mechanisms to select cases of interest and data that allow performance comparisons of different CADs requires further study.

One of our future goals is to define a methodology that reduces the complexity and repetition required to assess CAD systems. To this end, we intend to use the concept of CBIR for a comparison of graphical outputs (i.e., images) of CAD systems while considering their respective outputs as correct (Delamaro et al., 2013). The existence of public databases favors this approach because such databases often contain expert diagnoses that are associated with the images.

This paper presented the results of a systematic review that allowed the survey and analysis of the state of the art regarding the design, development and evaluation of systems for computer-aided diagnoses. We cataloged 98 CAD systems designed to automate various tasks to aid in disease diagnoses. These systems are described in the studies retrieved from five databases of published scientific papers.

Several groups worldwide have developed CAD systems. Thus, there are vast numbers of published papers analyzing diseases and various modalities of medical imaging, as presented here.

A non-systematic review may not fully explore the state of the art and can even require rework due to the lack of a detailed record on the performance of the review. In this context, the performance of a systematic review, specifically for CAD systems, provides both a general overview and specific details for interested groups. Furthermore, regular updates to the review and the ease of auditing presented results provide increased productivity in the bibliographic research.

The results confirm traditional metrics, which are based on true positives, true negatives, false positives and false negatives as the primary means to assess and compare the performance of CAD systems. ROC and FROC curves use methods derived from these metrics to assist in the assessment of system behaviors, given variations in their parameters.

However, these metrics and methods require the repetitive and exhausting participation of physicians and radiologists for verifying the accuracy of each version of a CAD system. While such participation is essential, the authors of this paper intend to focus on automating these verification tasks by using CBIR to compare the graphical output (i.e., images) of CAD systems with their respective database. In this future work, we will aim to determine an objective methodology for assessing CAD systems.

This study contributed an extensive literature review of the past six years on the state of the art of the design, development and assessment of CAD systems. We presented tasks of interest, relevant public databases of medical images, the main metrics and assessment methods, and a general analysis over the entire art.

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