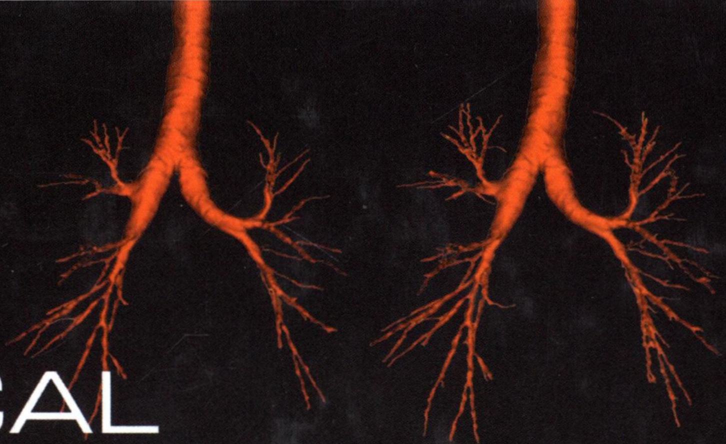

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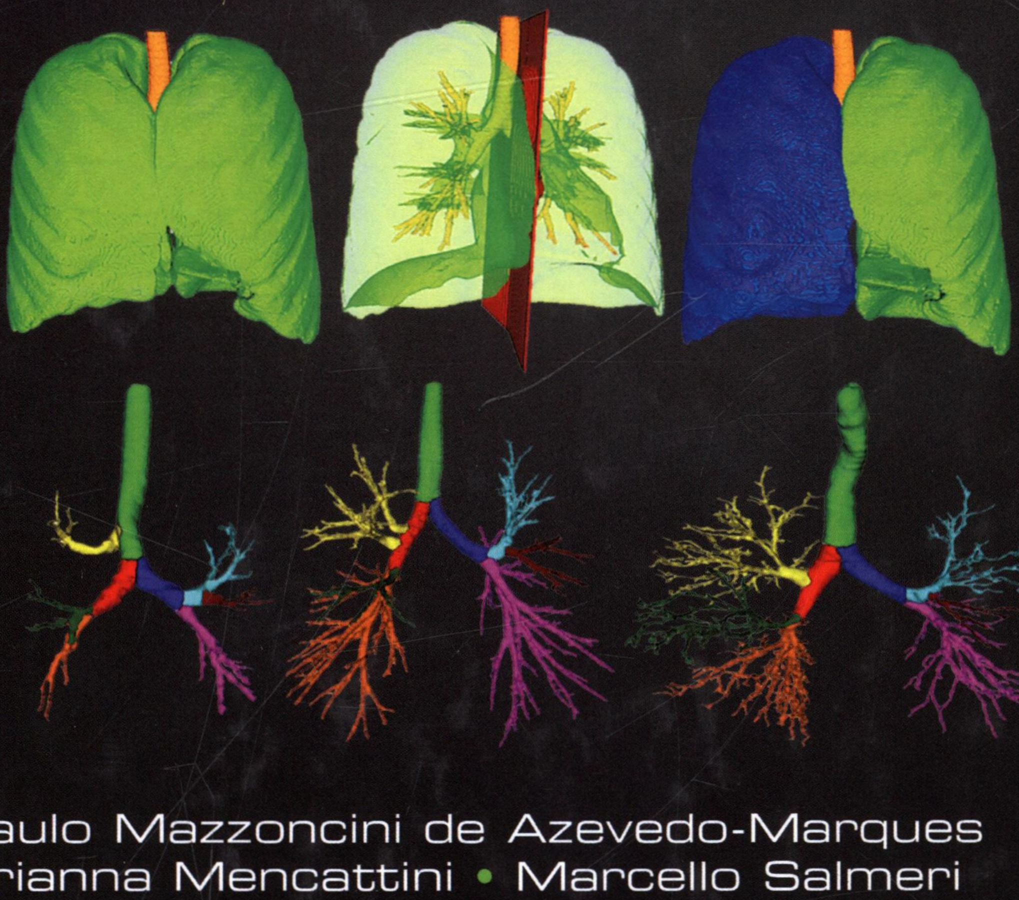
MEDICAL IMAGE ANALYSIS AND INFORMATICS

Computer-Aided Diagnosis and Therapy



Paulo Mazzoncini de Azevedo-Marques
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Rangaraj M. Rangayyan

BIOMEDICAL ENGINEERING

Medical Image Analysis and Informatics

Computer-Aided Diagnosis and Therapy

With the development of rapidly increasing medical imaging modalities and their applications, the need for computers and computing in image generation, processing, visualization, archival, transmission, modeling, and analysis has grown substantially. Computers are being integrated into almost every medical imaging system. *Medical Image Analysis and Informatics* demonstrates how quantitative analysis becomes possible by the application of computational procedures to medical images. Furthermore, it shows how quantitative and objective analysis facilitated by medical image informatics, CBIR, and CAD could lead to improved diagnosis by physicians. Whereas CAD has become a part of the clinical workflow in the detection of breast cancer with mammograms, it is not yet established in other applications. CBIR is an alternative and complementary approach for image retrieval based on measures derived from images, which could also facilitate CAD. This book shows how digital image processing techniques can assist in quantitative analysis of medical images, how pattern recognition and classification techniques can facilitate CAD, and how CAD systems can assist in achieving efficient diagnosis, in designing optimal treatment protocols, in analyzing the effects of or response to treatment, and in clinical management of various conditions. The book affirms that medical imaging, medical image analysis, medical image informatics, CBIR, and CAD are proven as well as essential techniques for health care.

- Leading researchers highlight the latest developments in medical image analysis, medical image informatics, CBIR, and CAD.
- The applications covered by *Medical Image Analysis and Informatics* are not limited to certain parts of the body or to certain diseases. Rather, a broad range of applications are investigated and described in detail.
- Several different medical imaging modalities and applications are included, satisfying the interests of biomedical researchers, neuroscientists, ophthalmologists, dentists, radiologists, oncologists, cardiologists, orthopedic specialists, dermatologists, gastroenterologists, and pathologists.
- *Medical Image Analysis and Informatics* presents a wide range of topics and applications that demonstrate the impressive impact of CAD and related fields on caring for the human body.
- The book illustrates how medical imaging, medical image analysis, medical image informatics, CBIR, and CAD are essential techniques for human health care.

K27338

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www.crcpress.com

6000 Broken Sound Parkway, NW
Suite 300, Boca Raton, FL 33487
711 Third Avenue
New York, NY 10017
2 Park Square, Milton Park
Abingdon, Oxon OX14 4RN, UK

ISBN: 978-1-4987-5319-7
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Medical Image Analysis and Informatics

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CRC Press
Taylor & Francis Group
Boca Raton London New York

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CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

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Printed on acid-free paper

International Standard Book Number-13: 978-1-4987-5319-7 (Hardback)

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Printed and bound in the United States of America by Sheridan

Medical Image Analysis and Informatics: Computer-Aided Diagnosis and Therapy

We dedicate this book
with gratitude and admiration
to medical specialists and clinical researchers
who collaborate with engineers and scientists
on computer-aided diagnosis and therapy
for improved health care.

Paulo, Arianna, Marcello, and Raj

Foreword on CAD: Its Past, Present, and Future

Computer-aided diagnosis (CAD) has become a routine clinical procedure for detection of breast cancer on mammograms at many clinics and medical centers in the United States. With CAD, radiologists use the computer output as a "second opinion" in making their final decisions. Of the total number of approximately 38 million mammographic examinations annually in the United States, it has been estimated that about 80% have been studied with use of CAD. It is likely that CAD is beginning to be applied widely in the detection and differential diagnosis of many different types of abnormalities in medical images obtained in various examinations by use of different imaging modalities, including projection radiography, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, nuclear medicine imaging, and other optical imaging systems. In fact, CAD has become one of the major research subjects in medical imaging, diagnostic radiology, and medical physics. Although early attempts at computerized analysis of medical images were made in the 1960s, serious and systematic investigations on CAD began in the 1980s with a fundamental change in the concept for utilization of the computer output, from automated computer diagnosis to computer-aided diagnosis.

Large-scale and systematic research on and development of various CAD schemes was begun by us in the early 1980s at the Kurt Rossmann Laboratories for Radiologic Image Research in the Department of Radiology at the University of Chicago. Prior to that time, we had been engaged in basic research related to the effects of digital images on radiologic diagnosis, and many investigators had become involved in research and development of a picture archiving and communication system (PACS). Although it seemed that PACS would be useful in the management of radiologic images in radiology departments and might be beneficial economically to hospitals, it looked unlikely at that time that PACS would bring a significant clinical benefit to radiologists. Therefore, we thought that a major benefit of digital images must be realized in radiologists' daily work of image reading and radiologic diagnosis. Thus, we came to the concept of computer-aided diagnosis.

In the 1980s, the concept of automated diagnosis or automated computer diagnosis was already known from studies performed in the 1960s and 1970s. At that time, it was assumed that computers could replace radiologists in detecting abnormalities, because computers and machines are better at performing certain tasks than human beings. These early attempts were not successful because computers were not powerful enough, advanced image processing techniques were not available, and digital images were not easily accessible. However, a serious flaw was an excessively high expectation from computers. Thus, it appeared to be extremely difficult at that time to carry out a computer analysis of medical images. It was uncertain whether the development of CAD schemes would be successful or would fail. Therefore, we selected research subjects related to cardiovascular diseases, lung cancer, and breast cancer, including for detection and/or quantitative analysis of lesions involved in vascular imaging, as studied by H. Fujita and K.R. Hoffmann; detection of lung nodules in chest radiographs by M.L. Giger; and detection of clustered microcalcifications in mammograms by H.P. Chan.

Our efforts concerning research and development of CAD for detection of lesions in medical images have been based on the understanding of processes that are involved in image readings by radiologists. This strategy appeared logical and straightforward because radiologists carry out very complex and difficult tasks of image reading and radiologic diagnosis. Therefore, we considered that computer algorithms should be developed based on the understanding of image readings, such as how radiologists can detect certain lesions, why they may miss some abnormalities, and how they can distinguish between benign and malignant lesions.

Regarding CAD research on lung cancer, we attempted in the mid-1980s to develop a computerized scheme for detection of lung nodules on chest radiographs. The visual detection of lung nodules is well-known as a difficult task for radiologists, who may miss up to 30% of the nodules because of the overlap of normal anatomic structures with nodules, i.e., the normal background in chest images tends to camouflage nodules. Therefore, the normal background structures in chest images could become a large obstacle in the detection of nodules, even by computer. Thus, the first step in the computerized scheme for detection of lung nodules in chest images would need to be the removal or suppression of background structures in chest radiographs. A method for suppressing the background structures is the difference-image technique, in which the difference between a nodule-enhanced image and a nodule-suppressed image is obtained. This difference-image technique, which may be considered a generalization of an edge enhancement technique, has been useful in enhancing lesions and suppressing the background not only for nodules in chest images, but also for microcalcifications and masses in mammograms, and for lung nodules in CT.

At the Rossmann Laboratories in the mid-1980s, we had already developed basic schemes for the detection of lung nodules in chest images and for the detection of clustered microcalcifications in mammograms. Although the sensitivities of these schemes for detection of lesions were relatively high, the number of false positives was very large. It was quite uncertain whether the output of these computerized schemes could be used by radiologists in their clinical work. For example, the average number of false positives obtained by computer was four per mammogram in the detection of clustered microcalcifications, although the sensitivity was about 85%. However, in order to examine the possibility of practical uses of CAD in clinical situations, we carried out an observer performance study without and with computer output. To our surprise, radiologists' performance in detecting clustered microcalcifications was improved significantly when the computer output was available. A paper was published in 1990 by H.P. Chan providing the first scientific evidence that CAD could be useful in improving radiologists' performance in the detection of a lesion. Many investigators have reported similar findings on the usefulness of CAD in detecting various lesions, namely, masses in mammograms, lung nodules and interstitial opacities in chest radiographs, lung nodules in CT, intracranial aneurysms in magnetic resonance angiography (MRA), and polyps in CT colonography.

The two concepts of automated computer diagnosis and computer-aided diagnosis clearly exist even at present. Therefore, it may be useful to understand the common features and also the differences between CAD and automated computer diagnosis. The common approach to both CAD and automated computer diagnosis is that digital medical images are analyzed quantitatively by computers. Therefore, the development of computer algorithms is required for both CAD and computer diagnosis. A major difference between CAD and computer diagnosis is the way in which the computer output is utilized for the diagnosis. With CAD, radiologists use the computer output as a "second opinion," and radiologists make the final decisions. Therefore, for some clinical cases in which radiologists are confident about their judgments, radiologists may agree with the computer output, or they may disagree and then disregard the computer. However, for cases in which radiologists are less confident, it is expected that the final decision can be improved by use of the computer output. This improvement is possible, of course, only when the computer result is correct. However, the performance level of the computer does not have to be equal to or higher than that of radiologists. With CAD, the potential gain is due to the synergistic effect obtained by combining the radiologist's competence with the computer's capability, and thus the current CAD scheme has become widely used in practical clinical situations.

With automated computer diagnosis, however, the performance level of the computer output is required to be very high. For example, if the sensitivity for detection of lesions by computer were lower than the average sensitivity of physicians, it would be difficult to justify the use of automated computer diagnosis. Therefore, high sensitivity and high specificity by computer would be required for implementing automated computer diagnosis. This requirement is extremely difficult for researchers to achieve in developing computer algorithms for detection of abnormalities on medical images.

The majority of papers related to CAD research presented at major meetings such as those of the RSNA, AAPM, SPIE, and CARS from 1986 to 2015 were concerned with three organs–chest, breast, and colon–but other organs such as brain, liver, and skeletal and vascular systems were also subjected to CAD research. The detection of cancer in the breast, lung, and colon has been subjected to screening examinations. The detection of only a small number of suspicious lesions by radiologists is considered both difficult and time-consuming because a large fraction of these examinations are normal. Therefore, it appears reasonable that the initial phase of CAD in clinical situations has begun for these screening examinations. In mammography, investigators have reported results from prospective studies on large numbers of patients regarding the effect of CAD on the detection rate of breast cancer. Although there is a large variation in the results, it is important to note that all of these studies indicated an increase in the detection rates of breast cancer with use of CAD.

In order to assist radiologists in their differential diagnosis, in addition to providing the likelihood of malignancy as the output of CAD, it would be useful to provide a set of benign and malignant images that are similar to an unknown new case under study; this may be achieved using methods of content-based image retrieval (CBIR). If the new case were considered by a radiologist to be very similar to one or more benign (or malignant) images, he/she would be more confident in deciding that the new case was benign (or malignant). Therefore, similar images may be employed as a supplement to the computed likelihood of malignancy in implementing CAD for a differential diagnosis.

The usefulness of similar images has been demonstrated in an observer performance study in which the receiver operating characteristic (ROC) curve in the distinction between benign and malignant microcalcifications in mammograms was improved. Similar findings have been reported for the distinction between benign and malignant masses, and also between benign and malignant nodules in thoracic CT. There are two important issues related to the use of similar images in clinical situations. One is the need for a unique database that includes a large number of images, which can be used as being similar to those of many unknown new cases, and another is the need for a sensitive tool for finding images similar to an unknown case.

At present, the majority of clinical images in PACS have not been used for clinical purposes, except for images of the same patients for comparison of a current image with previous images. Therefore, it would not be an overstatement to say that the vast majority of images in PACS are currently "sleeping" and need to be awakened in the future for daily use in clinical situations. It would be possible to search for and retrieve very similar cases with similar images from PACS. Recent studies indicated that the similarity of a pair of lung nodules in CT and of lesions in mammograms may be quantified by a psychophysical measure which can be obtained by use of an artificial neural network trained with the corresponding image features and with subjective similarity ratings given by a group of radiologists. However, further investigations are required for examining the usefulness of this type of new tool for searching similar images in PACS.

It is likely that some CAD schemes will be included together with software for image processing in workstations associated with imaging modalities such as digital mammography, CT, and MRI. However, many other CAD schemes will be assembled as packages and will be implemented as a part of PACS. For example, the package for chest CAD may include the computerized detection of lung nodules, interstitial opacities, cardiomegaly, vertebral fractures, and interval changes in chest radiographs, as well as the computerized classification of benign and malignant nodules. All of the chest images taken for whatever purpose will be subjected to a computerized search for many different types of abnormalities included in the CAD package, and, thus, potential sites of lesions, together with relevant information such as the likelihood of malignancy and the probability of a certain disease, may be displayed on the workstation. For such a package to be used in clinical situations, it is important to reduce the number of false positives as much as possible so that radiologists will not be distracted by an excessive number of these, but will be prompted only by clinically significant abnormalities.

Radiologists may use this type of CAD package in the workstation for three different reading methods. One is first to read images without the computer output, and then to request a display of the computer output before making the final decision; this "second-read" mode has been the condition that the Food and Drug Administration (FDA) in the United States has required for approval of a CAD system as a medical device. If radiologists keep their initial findings in some manner, this second-read mode may prevent a detrimental effect of the computer output on radiologists' initial diagnosis, such as incorrectly dismissing a subtle lesion because of the absence of a computer output, although radiologists were very suspicious about this lesion initially. However, this second-read mode would increase the time required for radiologists' image reading, which is undesirable.

Another mode is to display the computer output first and then to have the final decision made by a radiologist. With this "concurrent" mode, it is likely that radiologists can reduce the reading time for image interpretations, but it is uncertain whether they may miss some lesions when no computer output was shown, due to computer false negatives. This negative effect can be reduced if the sensitivity in the detection of abnormalities is at a very high level, which may be possible with a package of a number of different, but complementary CAD schemes. For example, although two CAD schemes may miss some lung nodules and other interstitial opacities on chest radiographs, it is possible that the temporal subtraction images obtained from the current and previous chest images demonstrate interval changes clearly because the temporal subtraction technique is very sensitive to subtle changes between the two images. This would be one of the potential advantages of packaging of a number of CAD schemes in the PACS environment.

The third method is called a "first-read" mode, in which radiologists would be required to examine only the locations marked by the computer. With this first-read mode, the sensitivity of the computer software must be extremely high, and if the number of false positives is not very high, the reading time may be reduced substantially. It is possible that a certain type of radiologic examination requiring a long reading time could be implemented by the concurrent-read mode or the first-read mode due to economic and clinical reasons, such as a shortage of radiologist manpower. However, this would depend on the level of performance by the computer algorithm, and, at present, it is difficult to predict what level of computer performance would make this possible. Computer-aided diagnosis has made a remarkable progress during the last three decades by numerous investigators around the world, including those listed in the footnote* and researchers at the University of Chicago. It is likely in the future that the concept, methods, techniques, and procedures related to CAD and quantitative image analysis would be applied to and used in many other related fields, including medical optical imaging systems and devices, radiation therapy, surgery, and pathology, as well as radiomics and imaging genomics in radiology and radiation oncology. In the future, the benefits of CAD and quantitation of image data need to be realized in conjunction with progress in other fields including informatics, CBIR, PACS, hospital

* Faculty, research staff, students, and international visitors who participated in research and development of CAD schemes in the Rossmann Laboratory over the last three decades have moved to academic institutions worldwide and continue to contribute to the progress in this field. They are H. P. Chan, University of Michigan; K.R. Hoffmann, SUNY Buffalo; H. Yoshida, MGH; R. M. Nishikawa, K. T. Bae, University of Pittsburgh; N. Alperin, University of Miami; F. F. Yin, Duke University; K. Suzuki, Illinois Institute of Technology; L. Fencil, Yale University; P. M. Azevedo-Marques, University of São Paulo, Brazil; Q. Li, Shanghai Advanced Research Institute, China; U. Bick, Charite University Clinic, Germany; M. Fiebich, University of Applied Sciences, Germany; B. van Ginneken, Radboud University, The Netherlands; P. Tahoces, University of Santiago de Compostella, Spain; H. Fujita, T. Hara, C. Muramatsu, Gifu University, Japan; S. Sanada, R. Tanaka, Kanazawa University, Japan; S. Katsuragawa, Teikyo University, Japan; J. Morishita, H. Arimura, Kyushu University, Japan; J. Shiraishi, Y. Uchiyama, Kumamoto University, Japan; T. Ishida, Osaka University, Japan; K. Ashizawa, Nagasaki University, Japan; K. Chida, Tohoku University, Japan; T. Ogura, M. Shimosegawa, H. Nagashima, Gunma Prefectural College of Health Sciences, Japan.

information systems (HIS), and radiology information systems (RIS). Due to the recent development of new artificial intelligence technologies such as a deep learning neural network, the performance of the computer algorithm may be improved substantially in the future, but will be carefully examined for practical uses in complex clinical situations. Computer-aided diagnosis is still in its infancy in terms of the development of its full potential for applications to many different types of lesions obtained with various diagnostic modalities.

Kunio Doi, PhD

Preface

Medical Imaging, Medical Image Informatics, and Computer-Aided Diagnosis

Medical imaging has been well established in health care since the discovery of X rays by Röntgen in 1895. The development of computed tomography (CT) scanners by Hounsfield and others in the early 1970s brought computers and digital imaging to radiology. Now, computers and digital imaging systems are integral components of radiology and medical imaging departments in hospitals. Computers are routinely used to perform a variety of tasks from data acquisition and image generation to image visualization and analysis (Azevedo-Marques and Rangayyan 2013, Deserno 2011, Dhawan 2011, Doi 2006, Doi 2007, Fitzpatrick and Sonka 2000, Li and Nishikawa 2015, Rangayyan 2005, Shortliffe and Cimino 2014).

With the development of more and more medical imaging modalities, the need for computers and computing in image generation, manipulation, display, visualization, archival, transmission, modeling, and analysis has grown substantially. Computers are integrated into almost every medical imaging system, including digital radiography, ultrasonography, CT, nuclear medicine, and magnetic resonance (MR) imaging (MRI) systems. Radiology departments with picture archival and communication systems (PACS) are totally digital and filmless departments. Diagnosis is performed using computers not only for transmission, retrieval, and display of image data, but also to derive measures from the images and to analyze them.

Evolutionary changes and improvements in medical imaging systems, as well as their expanding use in routine clinical work, have led to a natural increase in the scope and complexity of the associated problems, calling for further advanced techniques for their solution. This has led to the establishment of relatively new fields of research and development known as medical image analysis, medical image informatics, and computer-aided diagnosis (CAD) (Azevedo-Marques and Rangayyan 2013, Deserno 2011, Dhawan 2011, Doi 2006, Doi 2007, Fitzpatrick and Sonka 2000, Li and Nishikawa 2015, Rangayyan 2005, Shortliffe and Cimino 2014). CAD is defined as diagnosis made by a radiologist or physician using the output of a computerized scheme for image analysis as a diagnostic aid (Doi 2006, 2007). Two variations in CAD have been used in the literature: CADe for computer-aided detection of abnormal regions of interest (ROIs) and CADx for computer-aided diagnosis with labeling of detected ROIs in terms of the presence or absence of a certain disease, such as cancer.

Typically, a radiologist using a CAD system makes an initial decision and then considers the result of the CAD system as a second opinion; classically, such an opinion would have been obtained from another radiologist. The radiologist may or may not change the initial decision after receiving the second opinion, be it from a CAD system or another radiologist. In such an application, the CAD system need not be better than or even comparable to the radiologist. If the CAD system is designed to be complementary to the radiologist; the symbiotic and synergistic combination of the radiologist with the CAD system can improve the accuracy of diagnosis (Doi 2006, 2007).

In a more radical manner, one may apply a CAD system for initial screening of all cases and then send to the radiologist only those cases that merit attention at an advanced level; the remaining cases may be analyzed by other medical staff. While this process may be desirable when the patient population is large and the number of available medical experts is disproportionately small, it places heavier reliance and responsibility on the CAD system. Not all societies may accept such an application where a computational procedure is used to make an initial decision.

Medical image informatics deals with the design of methods and procedures to improve the efficiency, accuracy, usability, and reliability of medical imaging for health care. CAD and content-based image retrieval (CBIR) are two important applications in medical image informatics. CBIR systems are designed to bring relevant clinically established cases from a database when presented with a current case as a query. The features and diagnoses associated with the retrieved cases are expected to assist the radiologist or medical specialist in diagnosing the current case. Even though CBIR systems may not suggest a diagnosis, they rely on several techniques that are used by CAD systems and share some similarities. In this book, we present a collection of chapters representing the latest developments in these areas.

Why Use CAD?

At the outset, it is important to recognize the need for application of computers for analysis of medical images. Radiologists and other medical professionals are highly trained specialists. Why, when, and for what would they need the assistance of computers? Medical images are voluminous and bear intricate details. More often than not, normal cases in a clinical set up or details within a given image overwhelmingly outnumber abnormal cases or details. Regardless of the level of expertise and experience of a medical specialist, visual analysis of medical images is prone to several types of errors, some of which are listed in Table 1. The application of computational techniques could address some of these limitations, as implied by Table 2.

The typical steps of a CAD system are as follows:

1. Preprocessing the given image for further analysis
2. Detection and segmentation of ROIs
3. Extraction of measures or features for quantitative analysis
4. Selection of an optimal set of features
5. Training of classifiers and development of decision rules
6. Pattern classification and diagnostic decision making

Table 3 shows a simplified plan as to how one may overcome some of the limitations of manual or visual analysis by applying computational procedures.

The paths and procedures shown in Table 3 are not simple and straightforward; neither are they free of problems and limitations. Despite the immense efforts of several researchers, the development

TABLE 1 Causes of Various Types of Errors in Visual Analysis of Medical Images

Causes	Types of error
Subjective and qualitative analysis	Inconsistency
Inconsistencies in knowledge and training, differences in opinion, personal preferences	Inter-observer error
Inconsistent application of knowledge, lack of diligence, environmental effects and distraction, fatigue and boredom due to workload and repetitive tasks	Intra-observer error