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Computer-Aided Detection and Diagnosis at the Start of the Third Millennium

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Computer-aided diagnosis has been under development for more than 3 decades. The rate of progress appears exponential, with either recent approval or pending approval for devices focusing on mammography, chest radiographs, and chest CT. Related technologies improve diagnosis for many other types of medical images including virtual colonography, vascular imaging, as well as automated quantitation of image-derived metrics. A variety of techniques are currently employed with success, likely reflecting the variety of imagery used, as well as the variety of tasks. Most areas of medical imaging have had efforts at computer assistance, and some have even received FDA approval and can be reimbursed. We anticipate that the rapid advance of these technologies will continue, and that application will broaden to cover much of medical imaging. Acceptance of, and integration of computer-aided diagnosis technology with the electronic radiology practice is a current challenge. These challenges will be overcome, and we expect that computer-aided diagnosis will be routinely applied to medical images.

EVER SINCE it was possible to capture and display images on computers, people have been looking to the time when computers would receive a set of images and output a diagnosis.[1] The exponential growth of medical information dictates increased efficiency, making computer-enhanced or automated analysis of these data seem even more critical. Although this degree of automation still seems far away, there have been many advances that have brought us toward the goal of computer-aided detection and diagnosis. This article reviews the history and foundations of computer-aided diagnosis, beginning with a description of the goals of computer-aided detection and diagnosis as well as some of the basic common techniques. It also will discuss several of the state-of-the-art applications that have been developed.

In radiology, the task of image interpretation can be broken down into 3 essential parts: detection, description, and differential diagnosis. As medical images came to be acquired or displayed through the use of computers, the possibility of having computers perform any or all of these interpretive steps has been contemplated. This field became known as "Computer-Aided Diagnosis" or CAD. As it turns out, there has been more research and progress on detection than on either description or diagnosis. For familiarity and simplicity purposes, *CAD* will be used in this review to refer to both computer-aided detection and diagnosis, with context providing the meaning. There is a distinction between CAD and computerized image enhancement, and we will focus on computer techniques that attempt to detect, quantify, or estimate the probability of disease in radiologic images, with little attention to enhancement alone.

GOALS OF CAD

Detection of Abnormalities in Screening Examinations

For many years, it has been recognized that even the best human observers make errors in

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the interpretation of images. Errors may be attributed to many causes including imperfect perception or inaccurate analysis. These human shortcomings are exacerbated by radiologist fatigue, inexperience, and environmental factors. Although a perfect observer (human or machine) may never be possible, the use of computers to improve detection of abnormalities and to provide a list of probable diagnoses based on an objective analysis of the wealth of image-derived and clinical information should improve overall accuracy. For example, the fatigue factor is particularly prominent in screening examinations such as mammography and chest radiography. These high-volume screening examinations rarely contain pathologic findings, but the consequence of overlooking an uncommon but potentially cancerous lesion could be disastrous. Repetitive performance of lesion detection by a radiologist for these studies is, thus, both stressful and tedious. Yet, because these examinations are fairly standardized, and because the appearance of pathologies of interest (eg., cancer) have relatively few appearances, these types of examinations lend themselves to computer detection algorithms. The more specific the abnormality and focused the detection task, the better the computer algorithm is likely to be.

Description of Imaging Abnormalities

Detection is only the first step in characterization. Once detected, characterization then proceeds with identifying the precise anatomic extent of a lesion, its imaging properties (including size and other physical characteristics), as well as other features specific to the way in which the abnormality was imaged, such as contrast enhancement, margin appearance, and the "texture" of its density or signal. The radiologist learns many of the features of malignant masses[2] during training, and many of these same features (spiculation, border shape, density) are used by CAD algorithms to classify lesions.[3,4]

Measurement of Normal and Abnormal Structures

Although many radiologists resist the use of quantitative measurements to make diagnoses in everyday practice, quantitative tools have allowed increased precision in the diagnosis of some diseases, such as regional atrophy measurements in temporal lobe epilepsy[5] and Alzheimer's disease,[6] and computed tomography (CT) attenuation measurement of adrenal lesions.[7] It is not surprising that the first diseases to be diagnosed based on measurements are those in which anatomic changes are subtle or difficult to appreciate in individual images. As quantitative tools become more ubiquitous, it is possible that quantitative criteria for diagnosis will be developed for other diseases whose diagnosis may only be suggested by qualitative impressions today.

The above examples are measurements of structures that appear within the range of normal. An important task performed every day is the measurement of disease evolution—the development of abnormal structures. Currently, there is increased emphasis on "evidence-based medicine," increasing the need to develop methods for assessing the progression of disease and quantitative response to therapy that are objective and can be integrated into clinical practice and decision-making.

Diagnosis of Imaging Abnormalities

The most intellectually difficult aspect of image interpretation involves the synthesis of imaging information (including comparison with prior imaging examinations) and clinical information (demographic data, clinical history, and symptoms). For these complicated tasks, the ability of computers to quickly search vast databases of statistical data and retrieve clinical data certainly has great potential value, which has largely gone untapped.

TECHNIQUES AND COMPONENTS OF CAD APPLICATIONS

Most CAD applications consist of several components that aim to accomplish specific goals. Figure 1 provides an overall architecture of CAD systems. Although some systems may have little emphasis on one or more components, almost every system has recognizable elements of these pieces.

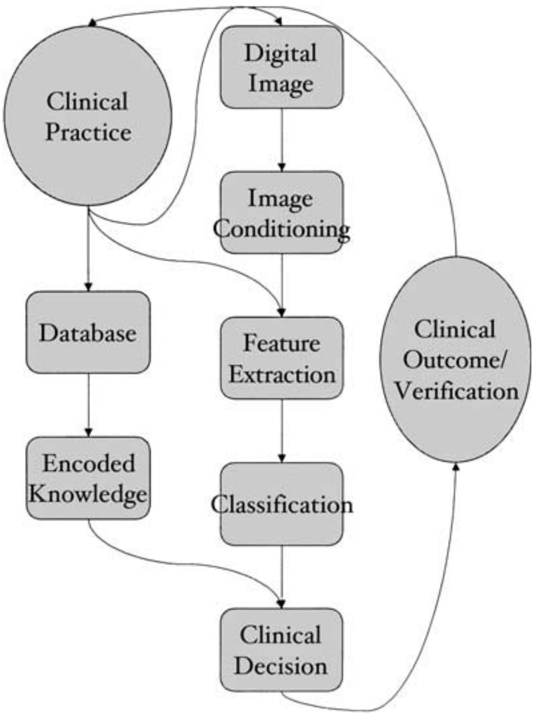

Fig 1. Functional component diagram of a CAD system. Not every component exists in every CAD system, but in most cases, at least a rudimentary function does exist.

Image Conditioning

The earliest forms of computer techniques to aid diagnosis were based largely on image filtering and enhancement methods. One could argue that adjusting window and level such as on a CT scanner is a basic form of computer-aided diagnosis. By adjusting to narrow window widths or measuring pixel values, one can diagnose some types of masses.[7] Additional image processing techniques that enhanced image features such as edges were the next step. These enhancement techniques could, for instance, increase lesion conspicuity to make findings more obvious. Pulmonary nodules are an especially appealing target, because a substantial fraction of pulmonary nodules are missed on screening chest x-rays[8,9]. Enhancing edges can improve observer sensitivity for detecting nodules.[10] The problem with many enhancement processes is the tendency to result in artifacts, which lead to excessive false-positive readings as well,[11] although it may be possible to reduce this problem using additional filters.[12]

The ability to adjust with window width and level significantly increases the amount of information that can be gained from digital images. Adaptive histogram equalization (AHE) is a technique that attempts to provide a single image in which the window width and level are optimized for each subregion of an image. Although this may be useful as an intermediate step in the process of CAD, it alone has not proven of value.[13]

Subtraction

It is often said that a comparison film is the radiologist's best friend. For CAD, the comparison film may be an essential companion. It is common clinical practice to display images side-by-side to directly compare change over time. In some arenas, such as digital-subtraction angiography, the time difference is very short. In this case, a mask image is obtained before contrast is injected. Images obtained while contrast is injected then are precisely super-imposed and subtracted from the mask image. The resulting image will show nonzero values only where a difference exists, which is where the contrast has appeared.[14]

Although it is more challenging to precisely align or "register" images taken months or years apart, it is feasible, particularly if the images are volumetric or 3-dimensional. This registration-subtraction technique has been applied to chest radiographs and mammograms as well as CT, magnetic resonance imaging (MRI) positron emission tomography (PET), and Single-photon emission computed tomography (SPECT), for the purpose of detecting subtle changes. Precise registration is obviously the key to the success of this method. Most registration methods use an iterative process in which an error metric is reduced until it is smaller than some acceptable value or until it fails to decrease after repeated tries. In cases in which images have the same contrast properties, the error metric often is the sum of the difference between individual pixels multiplied together (so that one is always summing positive values and to make large errors relatively more important). With appropriate precautions,[15] it

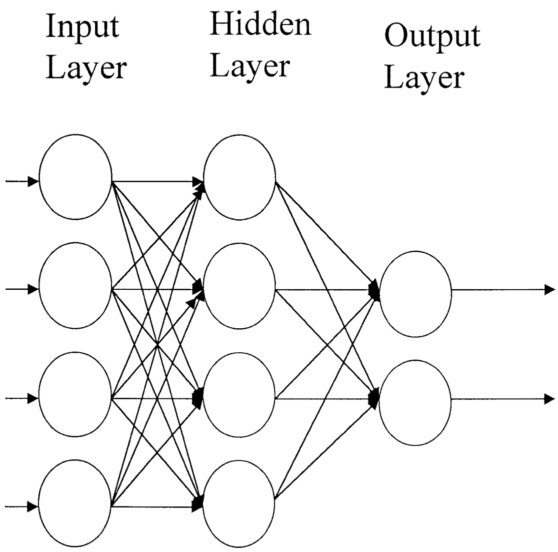

Fig 2. Diagram of a standard feed-forward neural network with 4 inputs, 2 outputs, and 1 hidden layer. For each input to a circle, there is a weighting for the signal that is transferred. These weights are adjusted until the proper outputs are obtained for all input patterns (or as near to the outputs as the network architecture and training permits).

is possible to get reliable registration for images of similar type.

When images have different contrast properties (eg, T_2 MRI image and a CT), the image difference metric fails. One early method[16] was the "head in hat" approach in which corresponding surfaces on the 2 images were identified, and the transformation that aligned the 2 surfaces was selected. Newer methods do not require the identification of corresponding structures (which can be time consuming and error prone) but use all voxels in the data set. Methods using pixel value ratios[17] and mutual information[18] have permitted precise registration of image with dissimilar contrast properties.

Pattern Recognition and Classification

Radiology and pathology are the most pattern recognition–oriented medical specialties. Training for both disciplines includes review of many thousands of images that portray diseases and normal anatomy. Ideally, through this training, pathologic processes are recognized, and abnormalities can be classified by applying this past experience to a current case. In theory, important patterns are "burned into" the neural pathways and "noise" excluded.

Statistical pattern recognition uses measurements and statistics from those measurements to classify example cases into categories. Syntactic (or structural) pattern recognition, however, attempts to identify rules that can classify patterns. Both methods of pattern recognition have been used to aid in development of differential diagnoses.[19]

Neural Networks

Neural networks are a form of pattern recognition but are treated separately because they have a very different structure from "standard" computer algorithms. Neural networks are modeled on the human brain—they have many "neurons" that produce output(s) based on a weighting of multiple inputs (Fig 2), possibly including examinations from multiple time points. The unique aspect of neural networks is that they can alter the weights by "training." During training, a set of inputs (ie, pathologic cases) is provided, along with the desired output (ie, the diagnosis). After a number of such training examples, the network is considered to have been trained and is ready for production. The appeal of this class of tools is that one need not know the appropriate weights for each input, because they are "learned" through the training process. Although it might seem appealing to simply provide a number of raw data sets to a network for training, the noise in most raw images tends to reduce accuracy. It also is possible to "overtrain" neural networks, leading to recognition of irrelevant features of the examples, rather than the truly general diagnostic features.[20]

Information Modeling and Probability

The above techniques are applied to the pixel information of an image. For a focused task like detecting breast cancer, this can result in increased accuracy of diagnosis. However, the accuracy of diagnosis ultimately is a function of not only the image information, but also requires a consideration of all disease entities that might exist in the patient and the associated probabilities. To properly assign those probabilities, one must have additional information that is unique to the patient as well as general information about disease probabilities. The probabilities for the patient then should be modified by findings (or lack thereof) noted in the image.

Many technologies have been developed for representing this additional information. A long-accepted method is to begin with observations of images and the frequency of those findings in a given disease, as well as information about the frequency of the disease. One then may apply Bayes' Rule for probability of causes to obtain an estimate of the probability that a given disease is present, given a certain finding.[21]

Another technique is to define vocabularies for representing nonpixel information in computer form. This is an entire field in itself and beyond the scope of this review. Basic principles include defining codes for disease concepts (eg, breast carcinoma) and methods to represent probabilities and conditions that modify those probabilities (eg, hormone therapy duration or family history). Including such clinical information as a patient's family history of breast cancer, age, and medical therapy have been proposed. A recent attempt to use age as one input did improve the performance of a mammography CAD system, although the difference was not statistically significant.[22]

A wide variety of technologies are available for CAD systems, and it appears that combinations will be required for optimal performance. Finding the best combination that is both reliable and performs well in a diverse clinical settings is a challenge that CAD scientists face.

EXAMPLE APPLICATIONS

In this section, a number of CAD applications (both laboratory and commercial) are described. This is by no means a complete listing of what has been developed. Rather, the focus is on covering the breadth of technologies used and on the breadth of imaging arenas. For that reason, the descriptions are brief, and the reader is encouraged to pursue the referenced articles in areas of interest.

Mammography—Screening and Diagnostic

Mammography is imaging of the breast, and there are 2 forms: screening and diagnostic. Screening mammography is focused on detection of masses that are likely to be cancerous in asymptomatic patients. Diagnostic mammography is performed on patients with symptoms—typically lumps, tenderness, or thickening of breast or skin tissues—or on patients with an abnormal screening mammogram that has been flagged by the radiologist for further workup. The probability of cancer is much higher in diagnostic mammography, and the challenge is largely one of classification (is the abnormality cancerous?) as opposed to screening, where detection is the primary challenge. Because the nature of these tasks is different, the CAD algorithms used are different.

It is well known that a substantial portion of breast cancers are "missed" on screening mammography. When CAD is applied to these missed cases, a substantial number were detected by CAD, and studies have suggested greater sensitivity to cancers might have been achieved.[23,24]

Breast cancers usually present as masses, architectural distortions, or microcalcifications on mammography. The algorithm for detecting each is different. In the case of calcifications, detection is relatively easy, but a number of benign processes also can produce calcification. Thus, it is in combination with classification of these abnormalities by size, shape, and distribution that leads to the diagnosis of cancer. CAD has enjoyed the greatest success in the detection of cancerous calcifications owing to the unique mammographic characteristics of cancer-associated calcifications.

Detection of masses is the next easiest task—but more difficult than one might expect. This is because currently, most CAD algorithms focus on a single projection at a time, whereas human performance is better when 2 views are provided.[25] Therefore, overlying structures can obscure portions of the boundary of a mass, which can make it less "masslike." Capitalizing on this information, Paquerault et al[26] reported improved mass detection when correlation of 2 views was implemented. There continues to be much effort on the problem of detecting masses, with a variety of techniques used.[27-32] Detection of architectural distortion is perhaps the most difficult task for CAD, because the current approach of using only a single projection hampers correlation of distortion between views. Only minimal literature is available on the detection of architectural distortion, with one example comparing left and right breasts.[33]

The first FDA-approved CAD products were for mammography.[34] Part of the FDA approval process required proof that the systems were effective. An example study of this type[35] showed that the accuracy of the CAD system with a radiologist was at least as good as 2 radiologists and superior to a single radiologist. Whereas some reports have suggested that CAD does not improve accuracy, it should be noted that these did not compare the system with a second reader, nor was it clear that the radiologists had fully accepted the system, because several cancers detected by the system were "rejected" by the radiologists.[36] Furthermore, for the same algorithm, selecting the cuing specificity (showing more false-positives to avoid false-negatives) can significantly affect CAD performance.[37]

Although detection is an important part of screening mammography, both screening and diagnostic mammography must correctly characterize detected masses as either benign or malignant. During training, the radiologist learns the features of malignant masse.[2] Many of these same features (spiculation, border shape, density) are used by CAD algorithms to classify lesions.[3,4] An important factor that also must be considered is that mammography CAD began with high-resolution film digitizers and only recently has become a digital imaging modality. It is important that algorithms developed for digitized films also function well with directly acquired digital images.[38]

Similar techniques have been used recently in the interpretation of ultrasound images of breast lesions.[39] It is possible that combining ultrasound scan and mammographic imaging will further increase diagnostic accuracy.

Chests—Radiography and CT

Chest radiography has a significant role as a screening examination. Detection of cancer is the primary task. Early attempts at chest CAD for nodule detection used edge-enhancing filters. The problem with most of the simple filtering methods was that they made not only true nodules more apparent, but they also made normal structures appear like nodules. To assist in reducing these false-positives, more sophisticated methods were added, including morphologic filters[12] and neural network.[40]

Another screening examination that has become more popular recently is the screening chest CT. The 3-dimensional nature increases the amount of information available, which increases the fatigue factor for humans, and increases the accuracy for computers. Most reports of systems for chest CT have focused on the detection of pulmonary nodules and tracking changes through time. Recent articles about CT nodule detection are included in the references.[41-43] In these cases, sensitivity and specificity are heavily dependent on the prevalence of disease in the studies included and vary with the size of nodule to be detected. Whereas most are not yet more accurate than a radiologist alone, they do help the radiologist in focusing in on regions of possible nodules, reducing the fatigue factor, and improving overall accuracy and efficiency in high-volume situations (much like screening mammography).

As noted above, the primary focus for CAD in thoracic imaging has been for nodule detection. However, neural networks also have been applied to the problem of providing a good differential diagnosis to ground glass opacities on computed radiography.[44]

Cardiovascular

PERFEX[45] is an example of a system for the interpretation of myocardial perfusion SPECT studies. This system detects perfusion defects in cardiac images, using rules about shape, size, location, and reversibility. In one large study, this system showed performance comparable to nuclear medicine experts for the detection and location of coronary artery disease. It uses a rule-based expert system based on extracted features.

Neuroradiology

The majority of applications seen in neuroradiology are for quantitation of disease rather than detection or diagnosis. Although measurement often is considered a minor role for radiologists, accurate assessment of extent of disease is crucial for accurate assessment of therapy effectiveness. Increasing use of automated quantification may allow earlier intervention and guidance of therapeutic options. In addition, as previously noted, precise measurement of structures has permitted diagnosis of some diseases, such as Alzheimer's disease and mesial temporal sclerosis.[5,6]

CT images of the head are obtained frequently to detect cerebral infarction and its complications (such as hemorrhage). This role is becoming increasingly important with the advent of therapies for stroke that have increased morbidity that depend on imaging appearance (hemorrhage and size/degree of abnormality). Maldjian et al[46] described an algorithm for assessing stroke size based on CT images. They used nonrigid image registration to an anatomic atlas to detect and measure hypodensity in the lentiform nuclei and insula. The algorithm produced 2 false-negative and 2 false-positive results from a group of 35 studies. The radiologist's readings at the time of the study had 5 false-negatives.

Virtual Colonography (and other virtual rendering methods)

Virtual colonography based on helical CT of the abdomen has become a popular imaging technique that competes with and complements fluoroscopic and endoscopic methods. In addition to yielding attractive 3-dimensional renderings, the data also can be processed by computer to automatically highlight regions that may represent cancerous or precancerous masses. Researchers have reported sensitivity for polyps ranging from 64% up to 100% with 1 to 5 false-positives for patients. The minimum size of the detected polyps varies, so comparison of studies is difficult. Similarly, the scanning and bowel preparation technique vary significantly. Although no product is commercially available, there are very promising results.[47,48]

Pediatric Radiology

A common task in pediatric radiology is the assignment of bone ages based on hand radiographs. This is done by matching the patient's hand radiograph to a set of standard images for patients of known ages. There are specific features of the bones of the hands that are markers for the biologic age of the patient, which are the key to proper assignment. There are reports of computer algorithms that can extract these features and match them to standardized images with good performance.[49]

Muskuloskeletal

One of the earliest reports of CAD used radiologists to extract features from images and then applied knowledge about frequencies (stored in a computer) to assign the probabilities of diseases.[21] Despite this early start, there is relatively sparse literature on the application of computer to detect or diagnose muskuloskeletal tumors or other diseases of the muskuloskeletal system. The greatest developments seem to be in the measurement of joint space narrowing for assessment of disease progress in the arthritides and to differentiate types of arthritis.[50]

DICOM AND CAD

No discussion of electronic medical imaging would be complete without a comment on how it relates to DICOM. In the case of CAD, there is a DICOM method for representing some of the information produced by a CAD system for mammographic images. The information can be encoded within a structured report, with specific codes for the type of finding(s), location(s), derived findings, and temporal changes. The full description can be obtained at the DICOM website: ftp:/medical.nema.org/medical/dicom/final/sup60 ft.pdf. Developing standards for other types of images such as chest CAD also are available at the medical.nema.org website, and also are based on the structured reports mechanism. In addition to providing structures for holding the output of CAD tools, DICOM provides some support for inserting CAD processing into clinical workflow.

FUTURE STEPS FOR CAD AND THE PRACTICE OF RADIOLOGY

Validation of CAD Methods

The first step in validating a CAD method is the application of the method to a locally collected set of test cases. However, it is essential that CAD methods be validated across a wide variety of image-producing equipment, as well as different patient populations. This is an expensive, difficult task. Once such a database of images and clinical information is created, it becomes a valuable resource for subsequent CAD investigations. This value has been recognized by the US Army as well as the National Cancer Institute (http://www3.cancer.gov/bip/iamwrkshp.htm).

Reimbursement

It is possible to be reimbursed for performing CAD on mammograms. Medicare issued HCPCS codes for payment, effective January 1, 2002. These include "76085 Digitization of film radiographic images with computer analysis for lesion detection and further physician review for interpretation, screening mammography." The corresponding code for CAD of diagnostic mammography is G0236. It is likely that other CAD procedures will receive reimbursement codes as FDA approval is given.

PACS and CAD

If CAD is to become an integral tool for image interpretation, it is crucial that it become integrated into workflow. As noted above, DICOM is developing portions of the mechanisms that will be required to integrate the CAD step to images after they are acquired. These will need to be embellished as CAD algorithms become more sophisticated, requiring image data from prior examinations of either the same or other modalities, and for collecting clinical information. It also is unlikely that the output will be a simple "yes-no" answer. Providing mechanisms for degree of certainty and reasoning also will be essential for acceptance of CAD, which is crucial for good performance.[36,37]

We do expect, however, that CAD will be implemented in a fashion similar to image analysis for pathology—that screening examinations focused on straightforward tasks (eg, detection of cancer on mammograms) will be increasingly automated with only occasional review by humans. As sophistication of algorithms increases, the number of examinations reviewed by humans will decrease. This will allow radiologists to focus on the more difficult cases, hopefully providing a more accurate and efficient practice of radiology.

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