Computer aided detection of nodules in low dose and thin slice lung CT

Poster No.: C-1053
Congress: ECR 2010
Type: Scientific Exhibit
Topic: Computer Applications - Without Subtopic
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Keywords: Computer Assisted Detection/Diagnosis, Image Processing, Lung Computed Tomography
Keywords: Computer applications, Computer Applications-General
DOI: 10.1594/ecr2010/C-1053

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Purpose

The purpose of the work here described is the development and validation of a Computer Aided Detection (CADe) system able to support radiologists in the identification of the various kinds of lung nodules [Fig.1] in the large amount of noisy images generated in screening programs, where low-dose settings are required and a thin-slice thickness is usually used.

The potential utility of such a system can be explained taking into account the following informations:

- Lung cancer is the leading cause of cancer-related mortality in developed countries [1, 2]. Only 10-15% of all men and women diagnosed with lung cancer live five years after diagnosis [2, 3] and no significant improvement has occurred in the last 20 years [4]. Early-stage cancer is asymptomatic, so more than 70% of patients diagnosed with lung cancer are in the advanced stages of the disease, when it's too late for effective treatments [5]. However the five-year survival rate for people who are diagnosed with early-stage lung cancer (stage I) can reach 70% [6].

- In this scenario, the implementation of screening programs for the asymptomatic high-risk population is an approach that is being tried to reduce the mortality rate of lung cancer. It was proved that screening programs with X-ray radiography don't lead to a reduction of the mortality rate [7 - 10], due to the low sensitivity of this technique in the identification of small, early-stage cancers.

- Lung cancer most commonly manifests itself with the formation of non-calcified pulmonary nodules. Computed Tomography (CT) is proved to be the best imaging modality for the detection of small pulmonary nodules, particularly since the introduction of the helical and multi-detector-row technologies [11 - 13]. Therefore CT-based screening trials are regarded as a promising technique for detecting small, early-stage lung cancers [14, 15].

- It has been demonstrated the ability of low dose and thin slice lung CT to make early diagnosis (at a stage of the disease in which it is still surgically treatable and curable), but it has and not yet been demonstrated its effectiveness in actual reduction in the total mortality linked to the disease, taking into account concurrent causes of death in smokers. The problem is therefore still open.

- From a technical point of view, these trials have shown that, because of the characteristics of images to be examined, the effort required to the radiologists is very big, comprising a lot of time for reporting and a high level of specialization in this field. The average number of images for these high-resolution CT are in fact up to 400, such images are very noisy because of the low dose of radiation required in screening and of the presence of non-neoplastic abnormalities typical of the high-risk subjects. Moreover,
the nodules to be found in the 2D projections are similar to sections of anatomical structures such as airways and blood vessels.

- It was indeed demonstrated that a large number of nodules (20-35%) risks to be missed in screening diagnoses [17].

In this scenario, CADe methods could be useful in order to support radiologists in the identification of early-stage pathological objects and the interpretation of diagnostic images is expected to benefit from the advances in computerized image analysis. Although the final diagnosis of medical images is made by the radiologists, they can use the output of a CADe system as a second opinion in detecting lesions and in making diagnostic decision. Despite a variety of well established procedures have already been presented to the scientific community, the problem of nodule identification in lung CT is still an open issue. The MAGIC-5 (Medical Applications in a GRID Infrastructure Connection, italian collaboration funded by INFN and MIUR) researchers have developed and validated different completely automated CAD methods optimized for the identification of the various kinds (in location, dimensions, geometrical shape) lung nodules in low-dose and thin-slice CT.
Fig. 0: Examples of internal (left) and juxtapleural (right) lung nodules.

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Fig. 0: Example of the goals of a CADe system.

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Methods and Materials

The lung CADe algorithms here presented have been developed by the researchers of the MAGIC-5 by means of CT scans made available by the Pisa centre of the ITALUNG-CT [18] screening trial.

In particular, the training data consisted of a set of low-dose lung CT scans acquired with a 4-slice spiral CT scanner according to a low-dose protocol (tube voltage: 140 kV, tube current: 20 mA, mean equivalent dose 0.6 mSv), with 1.25 mm slice collimation. Slices were reconstructed at 1 mm thickness, using a medium sharp reconstruction kernel. The number of slices per scan was approximately 300, each slice being a 512 by 512 pixel matrix, with pixel sizes ranging from 0.53 to 0.74 mm. The scans were annotated by experienced radiologists with a dedicated annotation and visualization [Fig.1, Fig.2] tool [19].

The general analysis strategy consists in three steps: lung volume segmentation, candidate nodule selection (ROI, Region Of Interest, Hunter), classification (rejection of false positive findings).

In order to optimize the detection of the various kinds of nodules (in terms of dimensions, geometry and position), a multi-method approach has been investigated, by means of three different original analysis approaches called CAM (Channeler Ants Model, in the following CAM CAD) [Fig. 3, Fig. 4], DE-PSN-VBNA (Dot Enhancement - Pleura Surface Normals - Voxel Based Neural Approach, in the following VBNA CAD) [Fig. 5, Fig. 6], RG-VP (Region Growing - Volume Plateau, in the following RG CAD) [Fig. 7, Fig. 8].

• CAM CAD: The method started with lung segmentation. The lung parenchyma was identified by means of a 3D region growing method and a wavefront algorithm for the definition of the lung surface on the inner side. The Channeler Ant Model [20] was used as a segmentation method for the vessel tree and the nodules candidates. Ant colonies were released on selected position of a 3D matrix, i.e. the anthill. Each ant behaves according to a predefined set of rules [20] and releases a quantity of pheromone while moving in the 3D environment defined by the lung volume. When the colony was extinct and no more voxels matched the required conditions to become anthills, the information provided by the pheromone map was analyzed. Ants explore (i.e. live in) a 3D environment described in terms of positions and intensities of voxels. Their life cycle is a sequence of atomic time steps, during which ants move from one voxel to one of its 26 neighbours. The behaviour of ants was defined by a set of rules that specify how they move in the environment, how much pheromone they release before moving to another location, when they reproduce or die.
The environment is defined by the voxel image intensities, which can be thought of as the amount of available food for the colony: therefore, voxel intensities should be progressively consumed when the number of visits increases. This mechanism, required to make the colony evolve and explore the environment, was implemented in a complementary way: whenever the limit to the maximum number of visits in a voxel was reached, the voxel was no more available as a destination. The ant colony started evolving from a voxel at the root of the vessel tree. When all the ants in the colony have died, the process stopped and the segmented object was removed from the original image and its coordinates were added to a list. In the remaining image, a voxel with intensity greater than a predefined threshold became the new anthill and a new 12 ant colony was deployed. If the number of voxels of an object was large with respect to the maximum expected size of a nodule, as it happens with the bronchial and vascular trees, the object was processed and smaller connected objects are looked for. The process finished when all the voxels inside the matrix with intensity above the threshold had been analyzed. From the segmented objects five features were extracted: number of voxels, maximum intensity, average intensity, standard deviation of intensity and sphericity. A feed-forward artificial neural network was implemented in order to classify the segmented objects. A limitation of the method is that nodules with diameter smaller than 3 mm attached to the vascular tree can not be detected.

**VBNACAD:** First, lung nodules were partitioned in two main classes, depending on their location in the lung. A nodule was labeled either as internal if fully contained in the lung parenchyma or as juxtapleural if connected to the pleura. The system dealt differently with internal and juxtapleural nodules, by means of two dedicated procedures: CADI for internal and CADJP for juxtapleural nodules. Both are three-step procedures [21, 22, 23, 24, 25]. The first step consists in the lung segmentation. An approach based on thresholding, region growing and morphological operators is implemented, once the scans have been isotropically resampled. In order to outline the shape of the pleura irregularities (including juxtapleural nodules), the lung boundaries were not smoothed. The identified lung mask, including vessels and airway walls, was used for CADI, whereas its boundary was used for CADJP. The second step consists in the candidate nodule selection. In the CADI the internal nodules were modeled as spherical objects with a Gaussian profile, following the approach proposed in [26]; the 3D matrix of data was filtered with a multi-scale filter function built to discriminate between spherical objects and objects with planar or elongated shapes. The local maxima of the 3D filtered matrix were the internal candidate nodule locations. A large number of false positives were included at this stage, above all crossings between blood vessels. In the CADJP, in order to identify juxtapleural candidate nodules, pleura surface normals were constructed and each voxel was assigned a score proportional to the number of 13 normals intersecting in it. To deal with noise, cylinders with Gaussian profile were considered
Instead of segments [27]. The local maxima of the 3D score matrix were the juxtapleural candidate nodule locations. A large number of FPs was found, mostly due to irregularities in the pleura surface (e.g. apical scars, pleural thickening and plaques) and movement artifacts. The third step consists in the FP reduction. An original procedure, the Voxel-Based Neural Approach [22, 23, 24, 25], was developed to reduce the number of FPs in the lists of internal and juxtapleural candidate nodules. First, a region of interest (ROI) including voxels belonging to the candidate nodule was defined from each location provided by the previous step. For internal candidate nodules, a simple procedure based on relative thresholding was implemented, while for juxtapleural candidate nodules a morphological opening-based algorithm was used. The basic idea is to associate to each voxel of a ROI a feature vector constituted by the intensity values of its 3D neighbors and the eigenvalues of the gradient matrix and of the Hessian matrix. Feature vectors were then classified by a three-layer feed-forward neural network which is trained to assign each voxel either to the nodule or normal tissue target class. A ROI was assigned a degree of suspicion p, defined as the percentage of voxels tagged as nodule by the neural classifier. The final list of findings was simply obtained by merging the output lists of findings generated by CADI and CADJP.

**RG CAD**: The system [28] consisted of three steps: 1) the lung parenchymal volume was segmented in the whole CT volume; 2) a region growing algorithm was iteratively applied to the segmented volume to detect candidate nodules; 3) a double-threshold and a neural network were applied to reduce false positives and classify the findings. The lung parenchymal segmentation started with a simple-threshold 3D region growing applied to the CT volume. The result is a binary mask of the respiratory system, containing the trachea, the bronchi, and the lungs. The next step was the segmentation of the external airways (trachea and bronchi) by a 3D region growing with wave-front simulation and suitable stop conditions, allowing a proper handling of the hilar region. Particular attention was given to detecting and solving the problem of the apparent fusion between the lungs, caused by partial-volume effects. 3D morphology operations ensured the accurate inclusion of all the nodules (internal, pleural, and vascular) in the segmented volume. The second step detected candidate nodules inside the segmented volume. This functionality was implemented by a region growing algorithm with an inclusion rule given by the logical AND of two rules: a voxel was included in the region if its density averaged with its first order neighbours was larger than a threshold t1, and a voxel was included in the region if its density was larger than a threshold t2. The threshold t1 was dynamically defined for each nodule candidate. Starting from an initial value, t1 was decreased to obtain a curve providing the volume as a function of the threshold. In general, this curve shows a decrease followed by a plateau due to difference in density between the background and the nodule candidate. From this curve it is possible to infer the best t1 value as the smallest in the range of the plateau. The t2 threshold and the starting
value of t\textsubscript{1} were chosen in order to maximize the detection rate (the fraction of selected nodules with respect to the total number of nodules diagnosed by the radiologist). The seed points were searched automatically as follows: the segmented volume is scanned until a voxel matching the inclusion rules (with thresholds t\textsubscript{2} and t\textsubscript{1}) was found; this voxel was used as seed point and the growth was started. Once the region was completely grown, it was removed from the scan and stored for further analysis. Then the search for new seed points was restarted. This process was iterated until no more seed points matching the inclusion rules were found. For each candidate nodule the following features were calculated: sphericity, ellipticity, maximum intensity, intensity standard deviation, Shannon entropy, volume, maximum radius. Almost all the FPs findings refer to candidates with too few voxels or to non-spherical candidates and could be easily ruled out by a simple threshold on the volume and the sphericity. A further reduction of false detections was obtained by means of a classification step carried out by a supervised two-layered feed-forward neural network, trained with a gradient descent learning rule and with a sigmoid transfer function. The output of the neural network was used as degree of suspicion for each candidate.

The validation test of these systems has been implemented both on a dataset of 20 independent (different but homogeneous than those used for developing the algorithms) scans of the same database (ITALUNG) and on scans of the public research databases ANODE09 (5 example and 50 test scans) [29] and LIDC (the first 84 scans made available by the LIDC consortium) [30].
**Fig. 0:** Functionality of the dedicated visualization and annotation tool.

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**Fig. 0:** How ants find the most efficient path to reach a destination. On the shortest path the pheromone density increases more quickly and therefore it attracts more and more ants. The process is non-linear.
**Fig. 0:** Original lung CT slice (left), number of counts (i.e. ants visits, middle) and amount of pheromone (right) after the ant colony extinction.
**Fig. 0:** Schemes of the VBNA based CADI (left) and CADJP (right).

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**Fig. 0:** Geometric schematization of the "Pleura Surface Normals" method for the search of juxtapleural nodule candidates.

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**Fig. 0:** Steps of analysis of the RGCAD.

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Fig. 0: Application of the "Region Growing" iterative algorithm.

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Results

The **FROC** (Free Receiver Operating Characteristic) curves for the three approaches show similar and satisfactory performance. Some examples are reported in Fig. 1, Fig. 2 and Fig. 3. In Fig. 4 is reported an example of juxta-pleural nodule as appears after the segmentation step of the CADJP and in Fig. 5 is reported an example of ROIs final classification by means of the VBNA method.

The **best results** are in the range of **75-80% of sensitivity with 5-10 FP/scan** (300-400 slices).

The systems work well also when applied to publicly available research **databases** with different characteristics (in terms of both acquisition and reconstruction parameters).

The most important peculiarity of this multi-approach system is that the **three approaches** show very **high complementarities** in the detection of the different categories of nodules, as shown by the results obtained in the ANODE09 competition [29, 31]. In this study [31] each CADe is assigned a score (evaluated as the average of sensitivities at 1/8, 1/4, 1/2, 1, 2, 4, 8 FP/scan) for the following kinds of nodules: small, large, isolated, vascular, pleural, peri-fissural. In the competition the **CAM** CAD obtained an overall score of 0.254, the **VBNA** of 0.293 and the **RG** CAD of 0.291, with, for example, the best performance of 0.467 obtained with **VBNA** CAD on isolated nodules and of 0.478 obtained with **RG** CAD on peri-fissural nodules. Moreover, by combining the results obtained on all nodules with the three approaches, the overall score increases to 0.522.
Images for this section:

**Fig. 0:** FROC curves obtained with the VBNACAD on different databases (red for ITALUNG, green for ANODE-example scans).

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**Fig. 0:** FROC curves obtained with the VBNACAD on different databases.

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Fig. 0: FROC curves obtained with the VBNACAD on different databases (blue for LIDC-4 radiologists, red for ITALUNG, green for ANODE-example scans).

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**Fig. 0**: Example of juxta-pleural nodule as appears after the segmentation step of the CADJP.

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Fig. 0: Example of ROIs final classification by means of the VBNA method.

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Conclusion

The CAM\textsuperscript{CAD}, VBNA\textsuperscript{CAD} and RG\textsuperscript{CAD} approaches show similar and satisfactory performance in the automated detection of lung nodules in different databases. They also show very good complementarities in the detection of different kinds of nodules.

A clinical validation of the complete overall CADe as a second reader has already being addressed and is being started by means of a dedicated annotation tool developed as a plugin of the OsiriX [32] imaging software [Fig. 1].
Fig. 0: Screenshot of the tool dedicated to the clinical validation of the CADe as second reader.

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