PLEURAL NODULE IDENTIFICATION IN LOW-DOSE AND THIN-SLICE LUNG COMPUTED TOMOGRAPHY

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Abstract

A completely automated system for the identification of pleural nodules in low-dose and thin-slice computed tomography (CT) of the lung has been developed. The \textit{directional-gradient concentration} method has been applied to the pleura surface and combined with a morphological \textit{opening}-based procedure to generate a list of nodule candidates. Each nodule candidate is characterized by twelve morphological and textural features, which are analyzed by a rule-based filter and a neural classifier. This detection system has been developed and validated on a dataset of 42 annotated CT scans containing 102 pleural nodules. The \textit{k}-fold cross validation has been used to evaluate the neural classifier performance. The system shows the 80% sensitivity to pleural nodules with 0.4 false positive findings per slice.

Keywords: Computer-aided detection (CAD); low-dose computed tomography (LDCT); thin-slice CT; lung nodule; directional-gradient concentration; morphological operators; neural networks.
1 INTRODUCTION

Lung cancer is one of the most lethal kinds of cancer worldwide. The overall 5-year survival rate is only 10-15% [1, 2] and no significant improvement has occurred in the last 20 years [3]. Non-calcified small pulmonary nodules are considered as the primary signs of early-stage lung cancers. Computed Tomography (CT) has been shown to be the most sensitive imaging modality for detecting small pulmonary nodules, particularly since the introduction of the multi-detector-row and helical CT technologies [4]. The efficacy of screening trial protocols based on low-dose CT with thin reconstructed slice thickness in reducing the lung cancer mortality rate are currently under investigation in many developed countries [5-8]. Depending on the screening trial protocol, the radiologists may have to identify even very small nodules, carrying out an extremely difficult and time-consuming task. Nodules are rather spherical or hemispherical objects that can be characterized by low CT values and/or low contrast. They may have CT values in the same range of those of blood vessels and airway walls and may be strongly connected to them or to the pleura surface. The nodule identification in screening CT is particularly difficult as low-dose CT images show a noisier appearance with respect to the standard-dose ones and an amount of image data as large as about 300 2D slices per scan may be generated in case thin reconstructed slice thickness is used.

To support radiologists in the challenging task of interpreting screening lung CT scans, researchers explore computer-aided detection (CAD) methods devoted to the automated identification of possibly pathological objects in the images. In this framework, an automated procedure for the detection of internal and sub-pleural lung nodules has already been developed by our group and described in [9] and [10]. The system we present in this paper is instead devoted to the automated identification of nodules deeply attached to the pleural surface, referred as pleural nodules. They are characterized by a rather hemispherical shape as they originate from the pleura surface and grow toward the lung parenchyma. Examples of the pleural nodule appearance in 2D CT slices and the corresponding volume rendering are shown in fig. 1.
This paper is structured as follows: the dataset we used in this analysis is described in sec. 2, the CAD algorithm is presented in sec. 3, and the final system results are reported in sec. 3.3.

2 The dataset of lung CT scans

The dataset of lung CTs used to develop, test and validate the CAD system has been acquired by means of a helical multi-slice CT scanner according to a low-dose protocol (LDCT) at a tube voltage of 140 kV, a tube current of 20 mA and a 1 mm reconstructed slice thickness.

The dataset used in this analysis consists of 42 CT scan. Each scan is stored as a DICOM (Digital Imaging and COmmunications in Medicine) file [11], and is constituted by $312 \pm 18$ 2D slices of $512 \times 512$ pixels each. The pixel size ranges from 0.54 to 0.74 mm, and the grey level intensity values are 4096 expressed in Hounsfield units (HU).

The dataset annotation has been provided by experienced radiologists participating to our research project. The software we developed for annotating the CT scans allows the radiologists to draw a circle enclosing a selected object on a CT slice; then, a 3D viewer is popped-up on demand to allow the size and location adjusting of the annotating sphere according to the nodule appearance in 3D. In the case of pleural nodules, the annotated diameters very often provide an overestimate of the nodule size. We considered for this study only the pleural nodules characterized by an annotated diameter greater than 5 mm, thus including in our dataset 102 solid pleural nodules. The average diameter of the nodule annotations used for this study is 7.6 mm with a 4.0 mm standard deviation.

3 The CAD system

The CAD strategy we implemented to identify the pleural nodules is shown in the block diagram reported in fig. 2. It is based on the following steps:

- a list of regions of interest (ROIs) is obtained by applying a two-step
procedure: first, the pleura is identified by an iso-surface triangulation technique; then, the ROIs are provided by the directional-gradient concentration method combined to a morphological opening operation;

- the FP findings populating the ROI list is ruled out by the following method: twelve geometrical and textural features are computed on the nodule candidate segmented out of each ROI; finally, a rule-based filter followed by a neural classification generate the list of CAD findings.

All steps of the analysis are detailed below.

3.1 Identification of nodule candidates: the ROI hunter procedure

A crucial task in the development of a CAD scheme for nodule detection is the initial selection of nodule candidates, which was carried out by means of a 3-step ROI hunter algorithm. For each CT scan it provides a list of the locations of the nodule candidates, expressed in terms of the $x$, $y$ and $z$ coordinates of their centers.

3.1.1 Identification of the pleura surface

The pleura has been identified as the separating surface between the lung parenchyma and the surrounding soft tissues. It has been determined according to an iso-surface triangulation technique.

Given a value $\mu_I$ (iso-value), the iso-surface corresponding to $\mu_I$ is defined as the set of points satisfying the equation $\mu(x, y, z) = \mu_I$. Such equation defines a surface that separates volumes having density greater than $\mu_I$ from
volumes having density lower than $\mu_I$. As shown in fig. 3 reporting the intensity distribution of $\mu(x, y, z)$ for one CT scan of our dataset, the lung parenchyma has a very low mean density (lower than $-800$ HU), while the soft tissues have a mean density around zero HU. To separate the lung parenchyma from the soft tissues, the value $\mu_I = -500$ HU can be used, as it corresponds approximately to the average between the mean densities of these tissues.

A discrete representation of an iso-surface can be obtained by approximating it by a set of small triangular facets. Such a procedure is called iso-surface triangulation. To represent the iso-surface obtained for $\mu_I = -500$ HU, we used the popular marching-cube algorithm [12, 13]. The output of the triangulation algorithm is a collection of triangular facets, which are clustered into connected components by forcing two triangles into the same component when they have at least one edge in common. The volume enclosed by each of these connected surfaces is evaluated. By convention, the sign is taken as positive if the intensity values inside the surface are above the threshold (and thus the region outside has values below the threshold), negative otherwise.

For example, the surface corresponding to the epidermis has a positive sign, since it is surrounded by air, which is surely below the threshold. The surface separating the lung parenchyma from the surrounding soft tissues is identified as the connected surface having the negative volume of largest magnitude. A mask for the lung parenchyma is obtained by flood-filling the volume inside such surface. At this stage, vessels and airway walls are not included in the mask. To include them, a procedure based on morphological was developed. In particular, the dilation operator with a spherical kernel of 10 voxels of diameter is applied to fill in the vessels and the airway walls, then, the erosion operator with spherical kernel of 20 voxels of diameter strongly erodes the mask border. Finally, the logical OR operation between the so-obtained mask and the original lung mask provides the final mask where the vessels and the airway walls are filled in, while maintaining the original shape of the lung mask border, i.e. the shape of the pleural nodule is not modified by this procedure.

3.1.2 Directional-Gradient Concentration (DGC)

To identify the ROIs where pleural nodules can be located, we implemented the directional-gradient concentration (DGC) method [14, 15], applied to the pleura surface. As pleural nodules are usually characterized by a convex surface, the inward-pointing fixed-length surface normal vectors $N(x, y, z)$ crossing the nodule surface tend to intersect within the nodule tissue. A 3D array, denoted as $A(x, y, z)$, counts the number of surface normals passing through each voxel, i.e. each voxel accumulates a score proportional to the number of surface normals that pass through it (see the 2D sketch in fig. 4). The larger the number of the line segments passing through a voxel, the higher the score the voxel has in the $A$ matrix. The local maxima in the $A$ matrix represent the convex regions characterizing pleural nodules or irregularities in the pleura surface. The DGC procedure has only one free parameter, which is the length of the surface normal vector. We fixed this parameter to $l=9$ mm after verifying that higher values of $l$ lead to an increase of noisy entries into the ROI list, whereas lower values of
Figure 4: Sketch of the DGC procedure: each voxel of the $A(x, y, z)$ matrix accumulates a score proportional to the number of surface normals that pass through it. For example, if 5 line segments pass through the central voxel of a pleural nodule, the score 5 will be assigned to that voxel.

Figure 5: Appearance of the mediastinal pleura in a CT scan: the flatness of the diaphragmatic pleura can be compared with the knurled surface representing the mediastinal pleura.

...do not allow the normal vector overlap in correspondence to large nodules.

We found out that many local maxima of the $A$ matrix are irregularities located in correspondence to the mediastinal pleura. As shown in fig. 5, the surface representing the mediastinal pleura in our CT scans is characterized by many folds and ridges, which are artifacts probably generated by the heart beating. The 3D DGC procedure is sensitive to these ridge-shaped artifacts, as they provide counts in the $A$ matrix in the same range of the nodules. However, as they have the principal direction corresponding to the maximum curvature along the $z$ axis, these artifacts will not affect a 2D slice-wise analysis. Thus we decided to combine the DGC method with a specific 2D procedure, as described in the following section.
3.1.3 Matching with the morphological opening-based procedure

A morphological opening operation has been implemented slice wise following the schema reported in fig. 6 and described below:

- the image obtained after the identification of the pleura surface is converted to a binary mask setting to 1 the region outside the pleura and to 0 the region inside;
- the morphological opening operator is applied slice wise to this mask by using a circular disk as structuring element;
- the opened image is then subtracted from the binary mask slice by slice;
- the sequence of 2D images obtained is recombined in a 3D array, denoted as \( B(x, y, z) \).

The only parameter introduced in this procedure is the size of the circular disk used as structuring element in the opening operation. We fixed the disk diameter to \( d_{\text{disk}} = 11 \) mm, as we have verified that using higher values of \( d_{\text{disk}} \) would include in \( B(x, y, z) \) unwanted portions of tissues, such as the section of the vascular tree near the lung hilum.

The logical AND operation is then implemented between the \( A \) and the \( B \) matrices. A peak-detector algorithm is applied to \( A \) AND \( B \) to detect the local maxima and create the list of ROIs, identified by the coordinates of their centers and sorted according to the value of the score reported in \( A \).

To assess the efficiency of our ROI hunter, we define as true positives (TPs) the nodule candidates that meet the radiologists’ diagnosis according to the following condition:

\[
\begin{align*}
\| x_{\text{rad}} - x \| & \leq R_{\text{rad}} \\
\| y_{\text{rad}} - y \| & \leq R_{\text{rad}} \\
\| z_{\text{rad}} - z \| & \leq R_{\text{rad}}
\end{align*}
\]

where \( \{(x_{\text{rad}}, y_{\text{rad}}, z_{\text{rad}}), R_{\text{rad}}\} \) are the center coordinates and the radius of the radiologists’ drawn circle, and \( (x, y, z) \) are the coordinates of the nodule candidate centers. All the other candidates are considered as false positives (FPs).
According to the above-mentioned definitions, the efficiency of the ROI
hunter is 94.1%, corresponding to 96 correctly identified pleural nodules out
of the 102 annotated in our dataset. At this stage the average number of FPs
per CT is 546.

3.2 False-positive finding reduction
The procedure we implemented to reduce the FP entries in the ROI list consists
in the classification of twelve morphological and textural features extracted from
each nodule candidate.

3.2.1 Feature extraction
To obtain a segmentation mask of each nodule candidate in order to extract
the features, we exploited the output of the previously described opening-based
procedure. We selected the 3D objects in the $B$ matrix which are connected to
the coordinates of each entry of the ROI list.

Twelve common features based on the geometrical and the textural character-
istics of the so segmented nodule candidates are computed:

1–4 the average, the standard deviation, the skewness and the kurtosis of the
density distribution of the nodule candidate, expressed in HU;

5-6 the minimum and the maximum value of the density distribution of the
nodule candidate, expressed in HU;

7 the volume of the nodule candidate, given by the number of voxels of the
segmented mask, converted to a physical volume (mm$^3$);

8 the volume of the 3D nodule candidate convex hull, estimated according
to the Qhull software [16, 17] and converted to a physical volume (mm$^3$);

9 the volume of the nodule candidate minimum enclosing ball, evaluated ac-
cording to the technique and the code developed by P. Kumar, J.S.B. Mitchell
and E.A. Yildirim [18].

10–12 the three eigenvalues of the covariance matrix of the nodule candidate
coordinates, which provide a rotational invariant measure of the object
extension along three orthogonal axes.

3.2.2 Feature classification
The procedure we implemented to reduce the FP entries from the list of nodule
candidates consists in a rule-based filter followed by a neural classification of
the feature vectors.

As a large number of FP findings are characterized by either a very small
or a very large size, a simple rule-based filter can easily eliminate them from
the list of nodule candidates. A double-threshold cut on the volume ($V$) of the
segmented nodule candidates and on the volume of their minimum enclosing
ball ($V_{\text{meb}}$) has been implemented. The lower and upper limits on $V$ and $V_{\text{meb}}$ have been \textit{a priori} determined according to the criterion that CAD has to be sensitive to pleural nodules in the size range limited by the values of $V$ and $V_{\text{meb}}$ of the smallest and of the largest nodule of the available dataset. Whenever a nodule candidate is characterized by either $V$ or $V_{\text{meb}}$ out of the allowed range it is considered as a FP and eliminated from further processing. This rule-based filter is able to eliminate the 26.8% of the FPs from the list of nodule candidates. The remaining 400 FP/scan on average are further analyzed by a neural classifier.

As the amount of the ROIs containing FPs (16782) is about two orders of magnitude larger than that of the ROIs containing nodules (96), only a small percentage of patterns derived from FP regions has to be considered in order to create a balanced dataset to train and validate the neural networks. To this aim we used a self-organizing map (SOM) [19]. Through an unsupervised learning procedure based on the \textit{winner-takes-all} rule, this kind of network clustersizes the input data into the cells of the Kohonen layer, according to a similarity criterion. We provided the entire FP dataset to a SOM, thus obtaining the clusterization of the FP feature vectors into $3\times3$ cells. By extracting a small percentage (1.5%) of the entries from each cell, we collected a sample of the FPs, which is representative of the entire FP dataset. This dataset of 246 FP patterns, in addition to the 96 nodule patterns, constitutes the dataset we used to train and validate the neural classification procedure.

The neural networks we implemented are standard supervised three-layered feed-forward neural networks (12 input, 14 hidden, 1 output units), trained with the back-propagation learning algorithm. The $k$-fold cross validation [20] with $k = 10$ has been implemented to evaluate the neural classifier performance. This method is used to determine how accurately a learning algorithm is able to predict the data it was not trained on. When using the $k$-fold method, the dataset is randomly partitioned into $k$ groups. The neural classifier is then trained $k$ times, using all data except those in the $k^{\text{th}}$ group, and then run on the $k^{\text{th}}$ set. The mean performance obtained over all $k$ sets is evaluated in terms of the Receiver Operating Characteristic (ROC) analysis [21]. We obtained an average area under the ROC curves $\text{AUC}= 0.88$, with a standard deviation $\sigma_{\text{AUC}}=0.07$.

We also computed the ROC curve for the complete dataset used in the 10-fold procedure, by collecting the neural output obtained on each fold. This ROC, which has an $\text{AUC}= 0.872 \pm 0.024$, is reported in fig. 7.

To classify the large set of FPs we had left apart during the sample extraction with the SOM (the 98.5% of FPs) we applied a simple meta-classification procedure. We assigned to each FP the average of the output obtained by the 10 trained neural classifiers. The ROC obtained has an $\text{AUC}= 0.865 \pm 0.024$, as reported in fig. 7. The error on the AUC is computed according to Ref. [22]. It can be noticed that the two values of AUC obtained are consistent, which confirms that the FP sample extracted with the SOM (1.5% of all FPs) is representative of the entire FP dataset, thus allowing a proper train and generalization capability of the neural classifiers.
3.3 Final system performance

We assessed the final system performance on the dataset of 42 CT scans containing 102 pleural nodules in terms of the Free-Rensponse Operating Characteristic (FROC) curve. The 94.1% (96/102) efficiency of the ROI hunter algorithm has been taken into account as a multiplicative factor to the values of sensitivities reported in the ROC (see fig. 7). The FROC curve obtained is shown in fig. 8. Our CAD system shows the 80% sensitivity with an average of 0.4 FP/slice.

4 Conclusions and discussion

We have developed a computerized method for the automated detection of pleural nodules on low-dose and thin-slice lung CT scans. This method consists of an initial selection of a list of nodule candidates, and the classification of the twelve features computed for each segmented nodule candidate. The system performance has been evaluated according to the 10-fold cross validation method on a dataset of 102 pleural nodules contained in 42 CT scans. The 80% sensitivity to the pleural nodules at a rate of 0.4 false positive findings per CT slice (FP/slice) is obtained.

As we have already developed a CAD system for internal and sub-pleural nodule detection [9,10], we decided to focus our research on pleural nodules only, as reported in this work. Since much more efforts in the literature have so far gone through the analysis of lung nodules independently of their location, we are
rather limited to have a vast performance comparison between our method and other CAD systems with the same purpose. Among the available CAD schemes, the one proposed by Paik et al. [14] in detecting clinically significant solid lung nodules using surface normal overlap method on datasets extracted from 8 chest CTs containing 84 nodules demonstrated the 80% sensitivity to nodules with 6 mm in diameter and larger at 1.3 FP/dataset. We could not convert this result in terms of FP/slice, as the number of slices analyzed for each dataset is not reported in [14]. In a study by Lee et al. [23] on pulmonary nodules, a conventional template matching was employed to detect nodules existing on the lung wall area. A dataset of 20 clinical cases has been considered. The system sensitivity to all types of nodules is 72% at 1.1 FP/slice. In particular, their system shows the 71% sensitivity to pleural nodules at 0.5 FP/slice. The ability in rejecting the 88% of FPs within the detected nodule candidates is also reported. At the same value of the sensitivity (71%) our system generates 0.19 FP/slice, and the corresponding FP rejection ability is 86%. However, a strict quantitative comparison between our system performance and those reported in [14] and [23] is precluded by the difference in the CT acquisition parameters and the small number of cases collected in the dataset used in each study.

Figure 8: The FROC curve obtained on the dataset of 42 CT scans containing 102 pleural nodules.
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