Validation, comparison, and combination of algorithms for automatic detection of pulmonary nodules in computed tomography images: the LUNA16 challenge

Arnaud Arindra Adiyoso Setio[a,1], Alberto Traverso[a,g,h,1], Thomas de Bel[n], Moira S.N. Berens[m], Cas van den Bogaard[n], Piergiorgio Cerello[h], Hao Chen[l], Qi Dou[l], Maria Evelina Fantacci[k,i], Bram Geurts[b], Robbert van der Gugten[m], Pheng Ann Heng[l], Bart Jansen[e,f], Michael M.J. de Kaste[m], Valentin Kotov[n], Jack Yu-Hung Lin[j], Jeroen T.M.C. Manders[m], Alexander Sóñora Mengana[d,e,f], Juan Carlos García Naranjo[d], Mathias Prokop[a], Marco Saletta[h], Cornelia M Schaefer-Prokop[a,c], Ernst T. Scholten[a], Luuk Scholten[n], Miranda M. Snoeren[b], Ernesto Lopez Torres[h], Jef Vandemeulebroucke[e,f], Nicole Walasek[n], Guido C.A. Zuidhof[m], Bram van Ginneken[a,o], Colin Jacobs[a]

[a] *Diagnostic Image Analysis Group, Radboud University Medical Center, Nijmegen, The Netherlands*
[b] *Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands*
[c] *Department of Radiology, Meander Medisch Centrum, Amersfoort, The Netherlands*
[d] *Centro de Biofísica Médica, Universidad de Oriente, Santiago de Cuba, Cuba*
[e] *Department of Electronics and Informatics, Vrije Universiteit Brussel, Brussel, Belgium*
[f] *iMinds, Zwijnaarde, Belgium*
[g] *Department of Applied Science and Technology, Polytechnic University of Turin, Turin, Italy*
[h] *Turin Section of Istituto Nazionale di Fisica Nucleare, Turin, Italy*
[i] *Pisa Section of Istituto Nazionale di Fisica Nucleare, Pisa, Italy*
[j] *Yan'an Xi Lu 129, 9th floor, Shanghai, China*
[k] *Department of Physics, University of Pisa, Pisa, Italy*
[l] *Department of Computer Science and Engineering, The Chinese University of Hong Kong, China*
[m] *Radboud University, Nijmegen, The Netherlands*
[n] *Institute for Computing and Information Sciences, Radboud University Nijmegen, Nijmegen, The Netherlands*
[o] *Fraunhofer MEVIS, Bremen, Germany*

Abstract

Automatic detection of pulmonary nodules in thoracic computed tomography (CT) scans has been an active area of research for the last two decades. However, there have only been few studies that provide a comparative performance evaluation of different systems on a common database. We have therefore set up the LUNA16 challenge, an objective evaluation framework for automatic nodule detection algorithms using the largest publicly available reference database, the LIDC-IDRI database. In LUNA16, participants develop their algorithm and upload their predictions on 888 CT scans in one of the two tracks: 1) the complete nodule detection track where a complete CAD system should be developed, or 2) the false positive reduction track where a provided set of nodule candidates should be classified. This paper describes the setup of LUNA16 and presents the results of the challenge so far. The impact of combining individual systems on detection performance is investigated. It is observed that the leading solutions employ convolutional networks and use the provided set of nodule candidates. The combination of these solutions achieves an excellent sensitivity of over 95% at fewer than 1.0 false positive per scan. Our observer study with four radiologists has shown that the best system detects nodules that have been missed by expert readers who originally annotated the LIDC-IDRI data. We release this set of additional nodules as an update to the LIDC-IDRI reference standard.

Keywords: pulmonary nodules, computed tomography, computer-aided detection, deep learning, challenges

1. Introduction

Lung cancer is the deadliest cancer worldwide, accounting for approximately 27% of cancer-related deaths in the United States (American Cancer Society (2016)). The NLST trial showed that three annual screening rounds of high-risk subjects using low-dose computed tomography (CT) reduced lung cancer mortality after 7 years by 20% in comparison to screen-

[1] These authors contributed equally to this work

ing with chest radiography (Aberle et al. (2011)). As a result of this trial and subsequent modeling studies, lung cancer screening programs using low-dose CT are currently being implemented in the U.S. and will likely be followed by other countries. One of the major challenges arising from the implementation of these screening programs is the enormous amount of CT images that must be analyzed by radiologists.

In the last two decades, researchers have been developing Computer-Aided-Detection (CAD) systems for automatic detection of pulmonary nodules. CAD systems are designed to make the interpretation of CT images faster and more accurate, hereby improving the cost-effectiveness of the screening program. The typical setup of a CAD system consists of: 1) preprocessing, 2) nodule candidate detection, and 3) false positive reduction. Preprocessing is typically used to standardize the data, restrict the search space for nodules to the lungs, and reduce noise and image artifacts. The candidate detection stage aims to detect nodule candidates at a very high sensitivity, which typically comes with many false positives. Subsequently, the false positive reduction stage reduces the number of false positives among the candidates and generates the final set of CAD marks.

Although a large number of CAD systems have been proposed (Bergtholdt et al. (2016); Torres et al. (2015); van Ginneken et al. (2015); Brown et al. (2014); Jacobs et al. (2014); Choi and Choi (2013); Tan et al. (2013); Teramoto and Fujita (2013); Cascio et al. (2012); Guo and Li (2012); Camarlinghi et al. (2011); Tan et al. (2011); Riccardi et al. (2011); Messay et al. (2010); Golosio et al. (2009); Murphy et al. (2009)), there have only been few studies providing an objective comparative evaluation framework using a common database. The reported performances of published CAD systems can vary substantially because different data sets were used for training and evaluation (Firmino et al. (2014); Jacobs et al. (2016)). Moreover, substantial variability among radiologists on what constitutes a nodule has been reported (Armato et al. (2009)). Consequently, it is difficult to directly and objectively compare different CAD systems. The evaluation of different systems using the same framework provides unique information that can be leveraged to further improve the existing systems and develop novel solutions.

ANODE09 was the first comparative study aimed towards evaluating nodule detection algorithms (van Ginneken et al. (2010)). This challenge has allowed groups to evaluate their algorithms on a shared set of scans obtained from a lung cancer screening trial. However, this study only included 50 scans from a single center, all of which were acquired by using one type of scanner and scan protocol. In addition, the ANODE09 set contained a limited number of larger nodules, which generally have a higher suspicion of malignancy. Evaluation on a larger and more diverse image database is therefore needed.

In this paper, we introduce a novel evaluation framework for automatic detection of nodules in CT images. A large data set, containing 888 CT scans with annotations from the publicly available LIDC-IDRI database (Armato et al. (2011)), is provided for both training and testing. A web framework has been developed to efficiently evaluate algorithms and compare the result with the other algorithms. The impact of combining multiple candidate detection approaches and false positive reduction stages was also evaluated.

The key contributions of this paper are: (1) we describe and provide an objective web framework for evaluating nodule detection algorithms using the largest publicly available data set; (2) we report the performance of algorithms submitted to the framework, as well as their combinations. We show that the combination of classical candidate detectors and a combination of deep learning architectures processing these candidates generates excellent results, better than any individual system; (3) we update the LIDC-IDRI reference standard by identifying nodules that were missed in the original LIDC-IDRI annotation process.

2. Data

The data set was collected from the largest publicly available reference database for lung nodules: the LIDC-IDRI database (Armato et al. (2011); Clark et al. (2013); Armato III et al. (2015)). This database is available from NCI's Cancer Imaging Archive[2] under a Creative Commons Attribution 3.0 Unported License. The LIDC-IDRI database contains a total of 1018 CT scans. CT images come with associated XML files with annotations from four experienced radiologists. The database is very heterogeneous: it consists of both clinical dose and low-dose CT scans, collected from seven different participating academic institutions, and a wide range of scanner models and acquisition parameters are included.

As recommended by Naidich et al. (2013); Manos et al. (2014) and the American College of Radiology (Kazerooni et al. (2014)), thin-slice CT scans should be

[2] https://wiki.cancerimagingarchive.net/display/Public/LIDC-IDRI

used for the management of pulmonary nodules. Therefore, we discarded scans with a slice thickness larger than 3 mm. Next to that, we excluded scans with inconsistent slice spacing or missing slices. This led to the final list of 888 scans. These scans were provided as MetaImage (.mhd) images that can be accessed and downloaded from the website (http://luna16.grand-challenge.org/).

Each LIDC-IDRI scan was annotated by experienced thoracic radiologists in a two-phase reading process. In the initial blinded reading phase, four radiologists independently annotated scans and marked all suspicious lesions as: nodule $\geq$ 3 mm; nodule $<$ 3 mm; non-nodule (any other pulmonary abnormality). For lesions annotated as nodule $\geq$ 3 mm, diameter measurements were provided. In a subsequent unblinded reading phase, the anonymized blinded results of all other radiologists were revealed to each radiologist, who then independently reviewed all marks. No consensus was forced.

In the 888 scans, a total of 36,378 annotations were made by the radiologists. We only considered annotations categorized as nodules $\geq$ 3 mm as relevant lesions, as nodules $<$ 3 mm and non-nodule lesions are not considered relevant for lung cancer screening protocols (Aberle et al. (2011)). Nodules could be annotated by multiple radiologists, annotations from different readers that were located closer than the sum of their radii were merged. In this case, position and diameters of these merged annotations were averaged. This resulted in a set of 2,290, 1,602, 1,186, and 777 nodules annotated by at least 1, 2, 3, or 4 radiologists, respectively. We considered the 1,186 nodules annotated by the majority of the radiologists (at least 3 out of 4 radiologists) as the positive examples in our reference standard. These are the lesions the algorithms of teams participating in LUNA16 should detect. Other findings (1,104 nodules annotated by less than 3 out of 4 radiologists, 11,509 nodule $<$ 3 mm annotations, and 19,004 non-nodule annotations) are considered “irrelevant findings” and marks on these locations are not counted as false positives nor as true positives in the final analysis. The same approach was used by (van Ginneken et al. (2010); Jacobs et al. (2016)). The motivation to exclude irrelevant findings in the evaluation is because they remain pulmonary abnormalities that could be important for different clinical diagnosis (Armato et al. (2011)) as a CAD mark on such a lesion is not a true false positive mark. It also alleviates the problem of disagreement on what constitutes a nodule (Armato et al. (2009); van Ginneken et al. (2010)).

3. LUNA16 challenge

The proposed evaluation framework is coined the LUng Nodule Analysis 2016 (LUNA16) challenge. LUNA16 invites participants to develop a CAD system that automatically detects pulmonary nodules in CT scans. The challenge provides the data set and the reference annotations described in Section 2. This data set can be used for training of the systems and the evaluation of the algorithms is performed on the same data set. This makes LUNA16 a completely open challenge. To prevent biased results as a result of training and testing on the same data set, participants are instructed to perform cross-validation in a particular manner detailed below. The LUNA16 website allows participants to submit the results. Submitted results are automatically evaluated and presented on the website. The next paragraphs describe the challenge in more detail.

3.1. Challenge tracks

The challenge consists of two separate tracks: (1) complete nodule detection and (2) false positive reduction.

The complete nodule detection track requires the participants to develop a complete CAD system and therefore, the only input to a system in this track is a CT scan.

In the false positive reduction track, participants are only required to classify a number of locations in each scan as being on a nodule or not. This corresponds to the so-called false positive reduction step in many published nodule CAD systems. For this track, a list of candidates is supplied to the participants, which is computed using existing nodule candidates detection algorithms (see Section 4.1). Phrased in this way, this problem can be seen as a typical machine learning task, where a two class (nodule/not-nodule) classification has to be performed. We included this track in the challenge to lower the barrier for participation for teams with experience in image classification tasks but no particular background on the analysis of chest CT scans. On the LUNA16 website, we included a tutorial how to extract cubes and patches around the nodule candidate locations in CT scans.

3.2. Cross-validation

Participants are required to perform 10-fold cross-validation when they use the provided LIDC-IDRI data both as training and as test data. The data set has been randomly split into ten subsets of equal size. The subsets can be directly downloaded from the LUNA16 website. To perform 10-fold cross-validation, participants should follow these guidelines (for fold N):

- split the data set into a test set and a training set. Subset N is used as test set and the remaining folds are used as the training set.
- for the 'false positive reduction' track, test and training candidates should be extracted on the corresponding test and training set;
- train the algorithm on the training set;
- test the trained algorithm on the test set and generate the result file;
- after iterating this process over all folds, merge the result files to get the result for all cases.

3.3. *Evaluation*

The results of the algorithms must be submitted online in the form of a comma separated value (csv) file. The csv file contains all marks produced by the CAD system. For each CAD mark, position (image identifier, x,y and z coordinate) and a score should be provided. The higher the score, the more likely the location is a true nodule.

A CAD mark is considered a true positive if it is located within a distance r from the center of any nodule included in the reference standard, where r is set to the radius of the reference nodule. When a nodule is detected by multiple CAD marks, the CAD mark with the highest score is selected. CAD marks that detect irrelevant findings are discarded from the analysis and are not considered as either false positive or true positive. CAD marks not falling into previous categories are marked as false positives.

Results are evaluated using the Free-Response Receiver Operating Characteristic (FROC) analysis (International Commission on Radiation Units and Measurements (2008)). The sensitivity is defined as the fraction of detected true positives (TPs) divided by the number of nodules in our reference standard. In the FROC curve, sensitivity is plotted as a function of the average number of false positives per scan (FPs/scan). For each scan, we took, at maximum, 100 CAD marks that were given the highest scores. The 95% confidence interval of the FROC curve are computed using bootstrapping with 1,000 bootstraps, as detailed in (Efron and Tibshirani (1994)). In order to evaluate and compare different systems easily, we defined one overall output score. The overall score is defined as the average of the sensitivity at seven predefined false positive rates: 1/8, 1/4, 1/2, 1, 2, 4, and 8 FPs per scan. The performance metric was introduced in the ANODE09 challenge and is referred to as the Competition Performance Metric (CPM) in Niemeijer et al. (2011).

The evaluation script is publicly available on the LUNA16 website and can thus be viewed and used by participants.

4. Methods

In this section we provide a brief description of the algorithms applied in the LUNA16 challenge. As of 31^{st} October 2016, seven systems have been applied to the complete nodule detection track and five systems have been applied to the false positive reduction track. First, the candidate detection algorithms that were used to generate candidates for false positive reduction track are presented in Section 4.1. Thereafter, the systems submitted to the complete detection system track are described in Section 4.2. Last, we described the systems submitted to the false positive reduction track in Section 4.3.

4.1. *Candidate detection*

This section describes the candidate detection algorithms applied in the challenge. All candidate detection algorithms were developed as part of published CAD systems (Murphy et al. (2009); Jacobs et al. (2014); Setio et al. (2015); Tan et al. (2011); Torres et al. (2015)), some of which are included in the complete nodule detection track. As candidates from multiple algorithms are likely to be complementary, we merged all candidates using the procedure described in Section 4.1.6. The list of merged candidates can be downloaded from the LUNA16 website and can be used by teams that want to participate in the false positive reduction track.

4.1.1. *ISICAD*

This generic nodule candidate detection algorithm was developed by Murphy et al. (2009). First, the image is downsampled from 512 × 512 to 256 × 256 with the number of slices reduced to form isotropic resolution. Thereafter, Shape Index (SI) and curvedness (CV) are computed at every voxel in the lung volume as follows:

$$SI = \frac{2}{\pi} \arctan(\frac{k_1 + k_2}{k_1 - k_2})$$

$$CV = \sqrt[2]{k_1^2 + k_2^2}$$

where k_1 and k_2 are principal curvatures computed using first and second order derivatives of the image with a Gaussian blur of scale $\sigma = 1$ voxel. After SI and CV are computed, thresholding on these values is applied to obtain seed points for nodule candidates. These seed points represent voxels which may lie on a nodule surface. Seeds are expanded using broader thresholds to form voxel clusters. To reduce the number of the clusters, clusters within 3 voxels are merged recursively. The center of the mass of the cluster is considered to be the point of interest.

4.1.2. SubsolidCAD

This candidate detection algorithm was built with the specific purpose to detect subsolid nodules, which are less common but more likely to be cancerous (Henschke et al. (2002)). The candidate detection algorithm by Jacobs et al. (2014) applies a double threshold density mask. The HU values commonly observed in subsolid nodules are used, ranging between -750 HU and -300 HU. Since partial volume effects may occur at the boundaries of the lungs, vessels and airways, a morphological opening using spherical structuring element (3 voxels diameter) is applied to remove these structures. Next, connected component analysis is performed. Components with a volume smaller than 34 mm^3 are discarded from the list of candidates as subsolid nodules with a diameter smaller than 5 mm do not require follow-up CT. The centers of the candidate regions are used as nodule candidate locations.

4.1.3. LargeCAD

This candidate detection algorithm (Setio et al. (2015)) was built with the specific purpose of detecting very large nodules. Large solid nodules (≥ 10 mm) have surface/shape index values or specific intensity range that is not captured by the two previously described nodule detection algorithms. An intensity threshold of -300 HU (usually corresponding to solid nodules) is applied in combination with multiple morphological operations. Thereafter, all connected voxels are clustered using connected component analysis and clusters with an equivalent diameter outside the range [8,40] mm are discarded.

4.1.4. ETROCAD

The applied method uses the system proposed by Tan et al. (2011). Isotropic re-sampling of the image to a voxel dimension of 1 mm^3 is applied in the preprocessing step. The nodule candidate algorithm consists of a nodule segmentation method based on nodule and vessel enhancement filters and a computed divergence feature to locate the centers of the nodule clusters. Three different set of filters (Li et al. (2003, 2004)) are applied to detect different types of nodules: isolated, juxtavascular, and juxtapleural nodules. To better estimate the location of the nodule centers and reduce the FP rate, the maxima of the divergence of the normalized gradient (DNG) of the image $k = \nabla(\overrightarrow{w})$ is used, where $\overrightarrow{w} = \frac{\overrightarrow{\Delta} L}{\|\overrightarrow{\Delta} L\|}$ and L is the image intensity. The enhancement filters and DNG are calculated at different scales in order to detect the seed points for different sizes of nodules.

Thresholding on the filtered image and DNG are applied to obtain the list of candidates. Different thresholds on the filtered image and the nodule-enhanced image are applied for isolated nodules, juxtavascular nodules, and juxtapleural nodules to get candidate locations. Finally, to ensure that a single nodule is represented by a single mark, cluster merging is performed.

4.1.5. M5L

The candidate detection algorithm proposed by Torres et al. (2015) consists of two different algorithms: lungCAM and Voxel-Based Neural Approach (VBNA).

LungCAM is inspired based on the life-cycle of ants colonies (Cerello et al. (2010)). The lung internal structures are segmented by iteratively deploy ant colonies in voxels with intensity above a predefined thresholds. The ant colony moves to a specific destination and releases pheromones based on a set of rules (Chialvo and Millonas (1995)). Voxels visited by ant colonies are removed and new ant colonies are deployed in unvisited voxels. Iterative thresholding of the pheromone maps is applied to obtain a list of candidates. The probability P_{ij} that a candidate destination is chosen is defined as:

$$P_{ij}(v_i \rightarrow v_j) = \frac{W(\sigma_j)}{\sum_{n=1,26} W(\sigma_n)}$$

where $W(\sigma_j)$ depends on the amount of pheromone in voxel v_j. The algorithm ends when all the ants in the colony have died.

VBNA uses two different procedures to detect nodules inside the lung parenchyma (Li et al. (2003); Retico et al. (2008)) and nodules attached to the pleura (Retico et al. (2009)). The nodules inside the lung parenchyma are detected using a dedicated dot-enhancement filter. Since nodules can manifest with a different size range, a multi-scale approach is followed (Li et al. (2003)). Nodule candidate locations are defined as the local maxima of the filtered image. The pleural nodules are detected by computing the surface normal at the lung wall. To build the normal, a marching cube algorithm is used. For each voxel inside the lung, the number of surface normals passing through are accumulated. Pleural candidates are defined as the local maxima of the accumulated scores.

4.1.6. Combining candidate detection algorithms

The combination of different CAD systems has been shown to improve the overall detection performance for nodule detection in chest CT (van Ginneken et al. (2010); Niemeijer et al. (2011)). The previously described candidate detection algorithms use different approaches to detect candidates and are likely to detect different set of nodules. In consequence, the combination of multiple algorithms may improve the detection sensitivity of nodules, and therefore, is a better baseline for the false positive reduction systems.

To combine the results of multiple candidate detection algorithms, each algorithm should provide the list of candidates. For each candidate, the position is given. First, we concatenated the list of candidates from all systems. Second, candidates located closer than 5 mm to each others are merged. Third, the position of the merged candidates are averaged. Candidates that are located outside the lung region are discarded, as they are not relevant for nodule detection. The lung region is determined based on the lung segmentation algorithm proposed by van Rikxoort et al. (2009). As the algorithm may exclude nodules attached to the lung wall, a slack border of 10 mm was applied.

4.2. Complete nodule detection system

Seven methods that were submitted to the complete nodule detection track are described in this section.

4.2.1. ZNET

ZNET uses ConvNets for both candidate detection and false positive reduction. As a preprocessing step, CT images are resampled to isotropic resolution of 0.5 mm. Candidate detection is extracted based on the probability map given by U-Net (Ronneberger et al. (2015)). U-net is applied on each axial slice. Before applying U-Net, the resampled input slice is resized to 512 × 512. The candidates are extracted based on the slice-based probability map output of the U-net. A threholding is applied to obtain candidate masks. The threshold was determined on the validation subset, maximizing the number of detected nodules. Thereafter, a morphological erosion operation with a 4-neighborhood kernel is used to remove partial volume effects. The candidates are then grouped by performing connected component analysis. The center of mass of the the components represent the coordinates of the candidates. The false positive reduction is described in Section 4.3.4. Both candidate detection and false positive reduction stages were trained in a cross-validation using provided folds.

4.2.2. Aidence

Aidence is a company developing computer assisted diagnosis tools for radiologists based on deep learning (`http://aidence.com/`). The LUNAAidence algorithm uses end-to-end ConvNets trained on a subset of studies from the National Lung Screening Trial (NLST) with additional annotation provided by in-house radiologists. The LUNA16 data set was used for validation purposes only, and was not used as training data.

4.2.3. JianPeiCAD

JianPeiCAD is a system developed by Hangzhou Jianpei Technology Co. Ltd., a company based on Hangzhou, China (`http://www.jianpeicn.com`). The algorithm follows the common two stage work-flow of nodule detection: candidate detection and false positive reduction. A multi-scale rule-based screening is applied to obtain nodule candidates. The false positive reduction uses a wide CNNs, which are trained using data augmentation to alleviate bias learning problem. The system was developed using in-house resources (Chinese patient CT images and CT devices from local-vendors) and LUNA16 data set was used as a further validation for patients outside China.

4.2.4. MOT_M5Lv1

The Multi Opening and Threshold CAD is a fully automatic CAD developed to be included into the M5L system (Torres et al. (2015)). The lung volume is obtained using 3D region growing, with a trachea exclusion and lung separation procedures. The candidate detection algorithm is developed based on the method proposed by Messay et al. (2010). Multiple gray level-thresholding and morphological processing is used to detect and segment nodule candidates. Several modifications to the sequence of threshold and opening radius, as well as to the merging procedure, were performed. Thereafter, a dedicated nodule segmentation method (Kuhnigk et al. (2006)) is applied to separate nodules from vascular structures during the segmentation step. The false positive reduction computes 15 features, ranging from geometrical features (e.g. radius, sphericity, skewness of distance from center) and intensity features (e.g. average, standard deviation, maximum, entropy). Classification is performed using feed-forward neural networks that consists of 1 input layer with 15 input units, 1 hidden layer with 31 units, and 1 output layer with 1 output unit.

4.2.5. VISIACTLung

This submission contains the results of the commercially available Visia$^{\text{TM}}$ CT Lung CAD system, version

5.3 (MeVis Medical Solutions AG, Bremen, Germany). This is an FDA approved CAD system designed to assist radiologists in the detection of solid pulmonary nodules during review of multidetector CT scans of the chest. It is intended to be used as an adjunct, alerting the radiologist after his or her initial reading of the scan to regions of interest (ROIs) that may have been initially overlooked.

4.2.6. ETROCAD

ETROCAD is a CAD system developed by Tan et al. (2011). The candidate detection algorithm is described in Section 4.1.4. The false positive reduction stage uses a dedicated feature extraction and classification algorithm. For each candidate, a set of features is computed: invariant features defined on a 3D gauge coordinates system, shape features, and regional features. The classification is performed using a feature-selective classifier based on artificial neural networks (ANNs) and genetic algorithms, called FD-NEAT.

4.2.7. M5LCAD

M5LCAD is a CAD system developed by Torres et al. (2015), which consists of two algorithms: lungCAM and VBNA. This CAD system uses the candidate detector algorithms described in section 4.1.5. The false positive reduction stage of LungCAM computes a set of 13 features for nodule candidate analysis, including spatial, intensity, and shape features. The set of features is used to classify the candidates using a feed-forward artificial neural network (FFNN). The FFNN architecture consists of 13 input neurons, 1 hidden layer with 25 neurons, and 1 neuron as output layer. The false positive reduction of VBNA performs the classification using a standard three-layered FFNN using the raw voxels as the feature vector (Retico et al. (2008, 2009)).

4.3. False positive reduction systems

Five methods that were applied to the false positive reduction track are described in this section.

4.3.1. CUMedVis

CUMedVis uses multi-scale 3D ConvNets developed by Dou et al. (2016). To tackle challenges coming from variations of nodule sizes, types, and geometry characteristics, a system that consists of three different 3D ConvNets architectures (*Archi-a*, *Archi-b*, *Archi-c*) is presented. Each subsystem uses an input image with different receptive field so that multiple levels of contextual information surrounding the suspicious location could be incorporated.

Archi-a has a receptive field of $20{\times}20{\times}6$. Three convolutional layers are used with 64 kernels of $5 \times 5 \times 3$, $5 \times 5 \times 3$, $5 \times 5 \times 1$, respectively. Thereafter, a fully-connected layer with 150 output units and a softmax layer are applied. *Archi-b* has a receptive field of $30 \times 30 \times 10$. After the first convolutional layer with 64 kernels of $5 \times 5 \times 3$, a max-pooling layer with kernel $2 \times 2 \times 1$ is used. Thereafter, two convolutional layers each with 64 kernels of $5 \times 5 \times 3$ are added. Finally, a fully-connected layer with 250 output units and a softmax layer are established. *Archi-c* has the largest receptive field of $40 \times 40 \times 26$. After the first convolutional layer with 64 kernels of $5 \times 5 \times 3$, a max-pooling layer with kernel $2 \times 2 \times 2$ is used. Thereafter, two convolutional layers each with 64 kernels of $5 \times 5 \times 3$ are added. Finally, a fully-connected layer with 250 output units and a softmax layer are established. The prediction probabilities from three ConvNets architectures are finally fused with weighted linear combination to produce the final prediction for a given candidate.

For pre-processing, voxel intensities are clipped into the interval from -1000 to 400 HU and normalized into the range from 0 to 1. To deal with the class imbalance between the false positives and nodules, translation (one voxel along each axis) and rotation (90^0, 180^0, 270^0 within the transverse plane) augmentations were performed on the nodules. The weights are initialized using a Gaussian distribution and are optimized using the standard back-propagation with momentum (Sutskever et al. (2013)). Dropout (Hinton et al. (2012)) strategy was applied during training. The system was implemented using Theano (Bastien et al. (2012)) and a GPU of NVIDIA TITAN Z was used for acceleration.

4.3.2. JackFPR

The proposed method uses similar multi-scale 3D ConvNets presented by (Dou et al. (2016)). It uses three 3D ConvNets architectures (*Archi-a*, *Archi-b*, *Archi-c*) described in Section 4.3.1. Several modifications were performed. Exponential activation units are used as the activation functions. Instead of combining the predictions of three ConvNets using linear combination, the fully-connected layers from three architectures were concatenated and were connected to a fully-connected layer with 128 output units. The last fully-connected layer is followed by a softmax layer to obtain the prediction.

The training was performed for 240 epochs with 1,024 iterations per epoch. Xavier initialization (Glorot and Bengio (2010)) was used as the weight initialization and Nesterov accelerated Stochastic Gradient Descent (SGD) was used. Cross-entropy loss, L2 regularization loss, and center loss were used as the cost function. Center loss penalizes the difference between a running average of learned features for each class and sample class features seen during the particular batch (Wen et al. (2016)). The learning rate was set to 0.005 for the first 5 epochs as a warming up, Thereafter, the learning rate was set to 0.01 and was reduced by 1/10 every 80 epochs. The model was trained on the provided subset. Data augmentation was performed and dropout was applied to combat over-fitting.

4.3.3. DIAG CONVNET

This method uses multi-view ConvNets proposed by Setio et al. (2016). For each candidate, nine 65 × 65 patches of 50 × 50 mm from different views are extracted. Each view corresponds to a different plane of symmetry in a cube and is processed using a stream of 2D ConvNets. The ConvNets stream consists of 3 consecutive convolutional layers and max-pooling layers. First convolutional layer is formed by 24 kernels of 5×5; second convolutional layer by 32 kernels of 3 × 3; third convolutional layer by 48 kernels of 3 × 3. Weights are initialized randomly and updated during training. The max-pooling layer is used to reduce size of patches by half. The last layer is a fully connected layer with 16 output units. Rectified linear units (ReLU) are used as the activation functions. The fusion of the different ConvNets is performed using the late fusion method (Prasoon et al. (2013); Karpathy et al. (2014)). Fully-connected layers from all streams are concatenated and are connected directly to a softmax layer. This approach allows the network to learn 3D characteristics by comparing outputs from multiple ConvNets streams. In this approach, all the parameters of the convolutional layers from different streams are shared.

Data augmentation is applied on candidates in the training set to increase the variance of presentable candidates. For each candidate, random zooming [0.9, 1.1] and random rotation [$-20^0, +20^0$] were performed. To prevent over-fitting during training, random positive and negative candidates with equal distribution were sampled in a batch of 64 samples. Validation was performed every 1,024 batches. Training was stopped when the area under the curve of receiver operating characteristic on the validation dataset does not improve after 3 epochs. Xavier initialization (Glorot and Bengio (2010)) was used as the weight initialization. The weights were optimized using RMSProp (Tieleman and Hinton (2012)). Evaluation was performed in 10-fold cross validation. Compared to the original work (Setio et al. (2016)), the submitted system uses an ensemble of three multi-view ConvNets trained using different random seed-points, averaging out biases from training using random samples. The system was implemented using Theano (Bastien et al. (2012)) and a GPU of NVIDIA TITAN X was used for acceleration.

4.3.4. ZNET

ZNET uses the recently published wide residual networks (Zagoruyko and Komodakis (2016)). For each candidate axial, 64 × 64 patches from the sagittal and coronal views are extracted. Each slice is processed separately by the wide residual networks. The predicted output values of the network for these three different slices were averaged to obtain the final prediction. The architecture uses 4 sets of consecutive convolutional layers. The first set consists of 1 convolutional layer with 16 kernels of 3 × 3. The second set consists of 10 convolutional layers with 96 kernels of 3 × 3. The third set consists of 10 convolutional layers with 192 kernels of 3 × 3. The forth set consists of 10 convolutional layers with 384 kernels of 3 × 3. The second to the forth sets are followed by max-pooling layer of 2 × 2. The last layer is a connected to a convolutional layer with 1 kernel of 8 × 8, resulting in a 1 × 1 output image.

Xavier initialization (Glorot and Bengio (2010)) was used for weight initialization and ADAM was used as the optimization method (Xu et al. (2015)). Leaky Rectified Linear Units were used as nonlinearities throughout the network. Data augmentation (flipping, rotation, zooming and translation) was applied not only on the training data set, but also on the test data set in order to improve the test set scores. The learning rate was reduced over time: learning rate is decreased by 90% after epoch 80 and epoch 125. All convolutional networks were implemented using Lasagne and Theano libraries (Dieleman et al. (2015); Bastien et al. (2012)). The training was performed on a computer cluster using large range of CUDA enabled graphics cards including the Tesla K40M, Titan X, GTX 980, GTX 970, GTX 760 and the GTX 950M.

4.3.5. CADIMI

This method uses multi-slice ConvNets. For each axial, sagittal and coronal view, three patches are extracted at three locations: the plane in the exact candidate location, as well as the planes from 2 mm of both directions on the remaining free axis (in x, y, z direction). The patches are concatenated as three-dimensional arrays. This results in patches of 52 × 52 × 3 mm, centered around the candidate location. The network consists of 2D ConvNets with consecutive convolutional layers and max-pooling. The first convolutional layer uses 24 channels of 5 × 5. The second convolutional layer uses

32 kernels of 3 × 3. The third convolutional layer uses 48 kernels of 3×3. The output of the last max-pooling is connected to fully-connected layer of 512 output units. ReLU was used as the activation function. The last fully-connected layer is connected to a softmax layer.

Training was performed one time using patches from all three views for 80 epochs. For each epoch, all positive patches and 20,000 random negative patches were used. In order to tackle the problem of data imbalance, data augmentation (vertical / horizontal flip and random cropping) was applied. During testing, 5 patches (1 center patch and 4 patches with [−4, +4] translation in two axes) are extracted from each view. These patches are processed using a single trained network and the predictions are averaged. Batch normalization was applied after each max-pooling layer to reduce overfitting. The weights were initialized using He uniform initialization (He et al. (2015b)). Nesterov accelerated SGD with a learning rate of 0.01, a decay of 0.001 and a momentum of 0.9 was used. The system was implemented using Lasagne and Theano libraries (Dieleman et al. (2015); Bastien et al. (2012)).

4.4. *Combining false positive reduction systems*

The combination of multiple classification methods, known as well as an ensemble method, has been used in many machine-learning problems to improve the prediction performance (Dietterich (2000)). As systems applied in the false positive reduction track use the same set of candidates, the impact of combining multiple methods could be evaluated. In this study, we combined CAD results from the systems in the false positive reduction track. The combination is performed by simply averaging the probabilities given by the systems. Such an ensemble approach is a common approach in optimizing the performance of deep learning architectures (Szegedy et al. (2014); He et al. (2015a)).

5. Results

In this section, we present the results achieved by all individual systems described in Section 4. The results of combining multiple algorithms are provided.

5.1. *Candidate detection*

Table 1 summarizes the performance of individual candidate detection algorithms and their top performing combinations. The sensitivities of the individual algorithms vary from 31.8% to 92.9%. When multiple candidate detection algorithms are combined, the sensitivity substantially improves up to 98.3% (1,162/1,186 nodules), higher than the sensitivity of any individual system. This illustrates the potential of combination of multiple candidate detection algorithms to improve the sensitivity of CAD systems.

5.2. *Complete nodule detection track*

The FROC curves of the systems on the complete nodule detection track are shown in Figure 1a. In this track, the best score is achieved by ZNET with a CPM of 0.811. Other systems show comparable performance. It is observed that the relatively large differences in terms of sensitivity at low FPs/scan substantially influence the overall scores of the systems.

5.3. *False positive reduction track*

The FROC curves of the systems on the false positive reduction track are shown in Figure 1b. The best average score is achieved by CuMedVis, with a CPM of 0.908. Table 2 shows all possible combinations of the systems. The sensitivity of the combined systems are higher than the sensitivity achieved by the best system. Although all false positive reduction systems are based on ConvNets, it is evident that combining ConvNets with different configurations still further improves the overall sensitivity as shown in Table 2.

5.4. *Analysis of false positives: observer study*

To evaluate the potential of CAD systems to detect nodules missed by human readers, and to elucidate the nature of the false positives of the CAD systems, an observer study was performed. In the observer study, CAD marks from the combination of false positive reduction systems were assessed to identify if there are additional nodules detected. The reading process was performed by four radiologists independently.

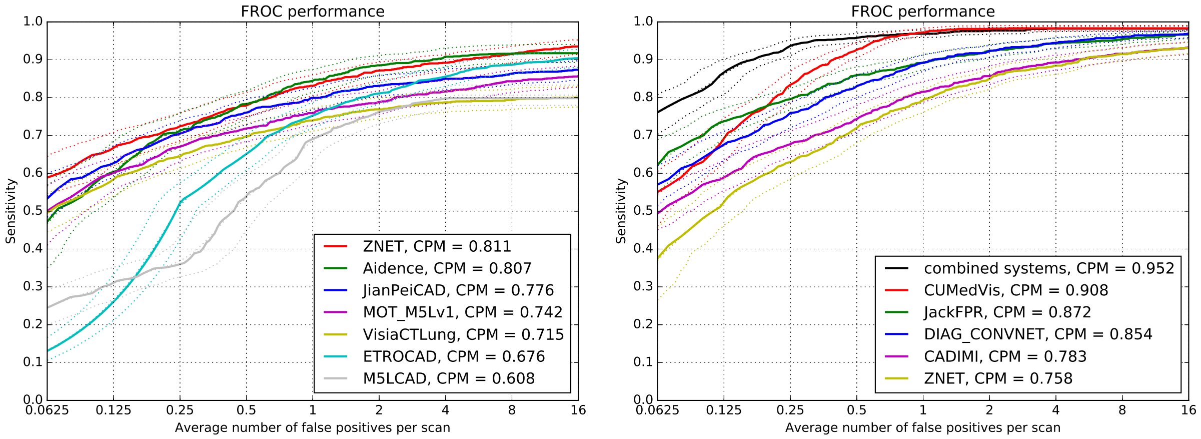
We extracted all CAD marks at 0.25 FPs/scan that were categorized as false positives. To reduce the workload of the radiologists, we eliminated CAD marks that were obviously false positives after a reading by research scientists. Thereafter, CAD marks on lesions that have been annotated in LIDC-IDRI, but were considered as false positives, were discarded. Most of these lesions were non-nodular and therefore, they are not well-captured by the defined hit criteria (radius of the corresponding lesion). This operation leads to a set of 127 marks that are potentially nodules. As a similar observer study was performed in our previous study (Jacobs et al. (2016)), marks which were already evaluated on this CT data were not read again and the scores of the four radiologists from the previous study were used. Last, we asked four radiologists to review and

System name	Combination	Sensitivity	Best single sensitivity	Difference sensitivity	Total number of candidates	Average number of candidates / scan
ISICAD (Murphy et al. (2009))	■□□□□	0.856			298 256	335.9
SubsolidCAD (Jacobs et al. (2014))	□■□□□	0.361			258 075	290.6
LargeCAD (Setio et al. (2015))	□□■□□	0.318			42 281	47.6
M5L (Torres et al. (2015))	□□□■□	0.768			19 687	22.2
ETROCAD (Tan et al. (2011))	□□□□■	0.929			295 686	333.0
	■■□□□	0.918	0.857	0.062	520 319	585.9
	■□■□□	0.898	0.857	0.041	328 742	370.2
	■□□■□	0.917	0.857	0.061	308 047	346.9
	■□□□■	0.959	0.929	0.030	524 108	590.2
	□■■□□	0.523	0.361	0.162	295 476	332.7
	□■□■□	0.869	0.768	0.101	274 900	309.6
	□■□□■	0.954	0.929	0.024	518 058	583.4
	□□■■□	0.834	0.768	0.066	59 359	66.8
	□□■□■	0.945	0.929	0.016	319 405	359.7
	□□□■■	0.942	0.929	0.013	297 030	334.5
	■■■□□	0.944	0.857	0.088	550 105	619.5
	■■□■□	0.954	0.857	0.098	530 942	597.9
	■■□□■	0.977	0.929	0.048	728 162	820.0
	■□■■□	0.934	0.857	0.078	339 229	382.0
	■□■□■	0.964	0.929	0.035	548 523	617.7
	■□□■■	0.967	0.929	0.038	529 404	596.2
	□■■■□	0.900	0.768	0.132	310 323	349.5
	□■■□■	0.964	0.929	0.035	545 204	614.0
	□■□■■	0.965	0.929	0.035	524 726	590.9
	□□■■■	0.954	0.929	0.024	326 274	367.4
	■■■■□	0.980	0.929	0.051	750 838	845.5
	■■■□■	0.983	0.929	0.054	732 901	825.3
	■■□■■	0.970	0.929	0.040	553 327	623.1
	■□■■■	0.965	0.857	0.108	559 543	630.1
	□■■■■	0.970	0.929	0.040	551 227	620.8
	■■■■■	0.983	0.929	0.054	754 975	850.2

Table 1: Results of five candidate detection systems and all possible combinations are shown. The filled squares indicate which systems have been included in the combination. The (combined) detection sensitivity and the number of candidates are listed.

System name	Combination	0.125	0.25	0.5	1	2	4	8	CPM	Best single CPM	Difference CPM
CUMedVis (Dou et al. (2016))	■□□□□	0.677	0.834	0.927	0.972	0.981	0.983	0.983	0.908		
JackFPR	□■□□□	0.734	0.796	0.859	0.892	0.923	0.944	0.954	0.872		
DIAG CONVNET (Setio et al. (2016))	□□■□□	0.669	0.760	0.831	0.892	0.923	0.945	0.960	0.854		
CADIMI	□□□■□	0.583	0.677	0.743	0.815	0.857	0.893	0.916	0.783		
ZNET	□□□□■	0.511	0.630	0.720	0.793	0.850	0.884	0.915	0.758		
	■■□□□	0.809	0.901	0.962	0.976	0.981	0.981	0.982	0.942	0.908	0.034
	■□■□□	0.831	0.917	0.965	0.979	0.981	0.981	0.981	0.948	0.908	0.040
	■□□■□	0.802	0.903	0.948	0.976	0.979	0.979	0.980	0.938	0.908	0.030
	■□□□■	0.831	0.927	0.968	0.976	0.979	0.981	0.981	0.949	0.908	0.041
	□■■□□	0.745	0.826	0.864	0.906	0.948	0.958	0.969	0.888	0.872	0.016
	□■□■□	0.717	0.797	0.858	0.895	0.932	0.947	0.959	0.872	0.872	0.000
	□■□□■	0.728	0.828	0.879	0.917	0.938	0.954	0.963	0.887	0.872	0.015
	□□■■□	0.550	0.680	0.796	0.869	0.912	0.938	0.959	0.815	0.854	-0.040
	□□■□■	0.616	0.737	0.831	0.888	0.931	0.953	0.964	0.845	0.854	-0.009
	□□□■■	0.602	0.732	0.812	0.852	0.884	0.913	0.946	0.820	0.783	0.037
	■■■□□	0.821	0.898	0.954	0.975	0.981	0.982	0.982	0.942	0.908	0.034
	■■□■□	0.816	0.897	0.945	0.970	0.980	0.980	0.980	0.938	0.908	0.030
	■■□□■	0.843	0.911	0.957	0.978	0.981	0.981	0.981	0.947	0.908	0.039
	■□■■□	0.817	0.912	0.954	0.968	0.975	0.979	0.982	0.941	0.908	0.033
	■□■□■	0.859	0.937	0.958	0.969	0.976	0.982	0.982	0.952	0.908	0.044
	■□□■■	0.820	0.907	0.946	0.968	0.976	0.981	0.981	0.940	0.908	0.032
	□■■■□	0.720	0.802	0.864	0.916	0.941	0.960	0.970	0.882	0.872	0.010
	□■■□■	0.736	0.835	0.891	0.924	0.945	0.969	0.973	0.896	0.872	0.024
	□■□■■	0.741	0.815	0.874	0.918	0.938	0.954	0.965	0.887	0.872	0.015
	□□■■■	0.635	0.777	0.839	0.888	0.929	0.954	0.965	0.855	0.854	0.001
	■■■■□	0.823	0.896	0.939	0.968	0.977	0.980	0.981	0.938	0.908	0.030
	■■■□■	0.846	0.912	0.949	0.971	0.977	0.981	0.982	0.946	0.908	0.037
	■■□■■	0.821	0.892	0.944	0.970	0.978	0.981	0.981	0.938	0.908	0.030
	■□■■■	0.830	0.912	0.947	0.964	0.973	0.979	0.981	0.941	0.908	0.033
	□■■■■	0.745	0.823	0.884	0.925	0.946	0.961	0.973	0.894	0.872	0.022
	■■■■■	0.836	0.896	0.940	0.965	0.976	0.981	0.982	0.939	0.908	0.031

Table 2: Results of five false positive reduction systems and all possible combinations are shown. The filled squares indicate which systems have been included in the combination. The average sensitivity (CPM) and the difference compared to the best single CPM are shown.



(a)

(b)

Figure 1: FROC curves of the systems in (a) nodule detection track and (b) false positive reduction track. Dashed curves show the 95% confidence interval estimated using bootstrapping.

Table 3: Overview of the observer study on 222 false positives at 0.25 FPs/scan. The table shows the number of false positives that are accepted by the radiologists as nodules ≥3 mm at different agreement levels. The number of false positives that are not accepted as nodules ≥3 mm, but are accepted as nodules <3 mm, are also included.

Category	Number
nodule ≥3 mm - at least 1	N_0
nodule ≥3 mm - at least 2	N_1
nodule ≥3 mm - at least 3	N_2
nodule ≥3 mm - at least 4	N_3
not nodule ≥3 mm - nodule <3 mm	N_4

annotate the remaining marks as: nodule $\geq$ 3 mm, nodule < 3 mm, or false positives. Measurement tools were available to radiologists during the process in order to allow size evaluation.

A summary of the observer study is shown in Table 3. Among 127 CAD marks, N_0, N_1, N_2, and N_3 CAD marks are accepted as nodules $\geq$ 3 mm by at least 1, 2, 3, or 4 radiologists, respectively; N_4 out of N_5 remaining CAD marks are considered as nodule < 3 mm. Examples of nodules found in this observer study are shown in Figure 2c. We shared the set of additional nodules in the LUNA16 website (LINK) to be used for further development of CAD systems.

6. Discussion

In this study, we presented a novel evaluation framework for automatic nodule detection algorithms, which is coined as LUNA16. The aim of the study is to supply the research community a framework to test and compare algorithms on a common large database with a standardized evaluation protocol. This allows the community to objectively evaluate different CAD systems and push forward the development of state of the art nodule detection algorithms. The submitted systems are described and the performance is evaluated. We showed that the combination of multiple false positive reduction algorithms applied on a combined set of candidates obtain an excellent performance, outperforming any individual system.

Candidate detection plays an important role, as it determines the maximum detection sensitivity of a CAD system. The algorithms should ideally detect all nodules with an acceptable amount of false positives. Table 1 shows that individual candidate detection algorithms achieve a detection sensitivity between 31.8% to 92.9%. The detection of nodules with a wide range of morphological characteristics is still a challenging task for any single algorithm. Combining different candidate detection algorithms improves the sensitivity up to 98.3%. This confirms the importance of combining candidate detection algorithms to improve the detection performance of CAD systems.

In the complete nodule detection track, a total of seven systems were evaluated. Diverse methods were applied and different set of data were used for training. When evaluated using the same data set, the detection sensitivity ranges between 69.1% and 91.5% at 1 and 8 FPs/scan, as shown in Figure 1a. Top three systems make use of ConvNets for their detection algorithms. While the variability of the performance is determined by the underlying methods, it is also affected by the training data that is used to develop the system (see also

Table 4). This suggests the need of a standardized training data set for appropriate comparison of algorithms.

In the false positive reduction track, different systems for false positive reduction are evaluated, given a common set of candidates and training data. A total of five systems were evaluated. ConvNets are used as the prediction model for all systems, which is aligned with the recent trend in adapting deep learning in the medical image analysis domain. As shown in Figure 1b, all systems achieve detection sensitivity between 79.3% and 98.3% at 1 and 8 FPs/scan. As the underlying method is similar, one could hypothesize that there could be little to no benefit when these systems are combined. However, the results show that combining multiple ConvNets systems substantially improves the detection performance (black curve on Figure 1b). The detection sensitivity of over 95.0% is achieved at fewer than 1 FP/scan. Although all the methods are based on ConvNets, the differences in network parameters, such as the selected architectures and the input patches, makes these systems complementary in terms of the prediction.

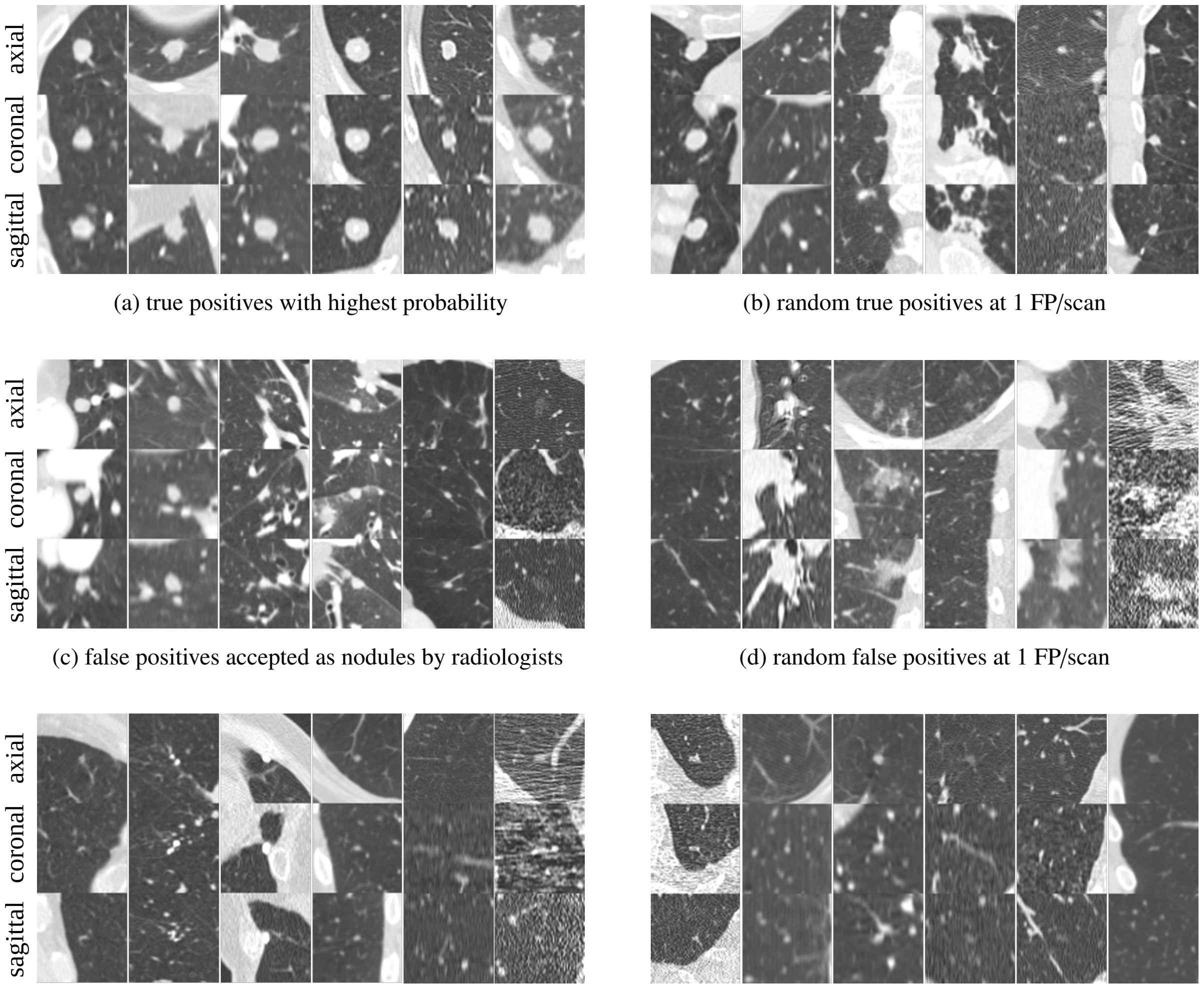
The observer study shows that some false positives detected by the CAD systems are nodules that were missed during the manual annotations of LIDC-IDRI. The majority of these nodules are small nodules that were overlooked, nodules that were missed because there were multiple nodules in the corresponding scans, or nodules that were part of a more complex abnormality, for example an area of consolidation. While these nodules may be found during follow-up, detecting them early provides more information that may be clinically important (e.g. determine whether a nodule is growing or not).

Examples of lesions detected or missed by the combined CAD system are shown in Figure 2. Nodules with a wide range of morphological characteristics are detected at 1 FP/scan, showing that ConvNets are capable to capture morphological variation of nodules in the network. Most nodules detected with a high probability are large nodules. These nodules are likely to be malignant and should not be missed by CAD. Beside false positives that have been accepted as true nodules by the radiologists in our observer study, most of the false positives are large vessels, mediastinal structures, scarring, and spinal abnormalities. Other false positives are caused by motion artifacts and extremely noisy scans. The remaining nodules that were missed by the CAD system at 1 FP/scan consist of small nodules or nodules with irregular shapes. Most of the small nodules were missed by the candidate detection algorithms. Improving the robustness of the candidate detection algorithms may improve the performance even further.

For completeness, the performance of other CAD systems that use LIDC-IDRI data are summarized in Table 4. For each CAD system, we listed the number of scans used in validation data set, nodule inclusion criteria (e.g. nodule type, nodule size, agreement levels), number of nodules, and reported CAD performance. While the CAD performance is difficult to be straightforwardly compared as different data set was used, the table shows a broader context of the reported CAD performance in the literature. The CAD systems presented in (Jacobs et al. (2016)) are not listed in this table as these CAD systems also participated in the LUNA16 challenge and hence are already described in this paper.

This study has limitations. As the LIDC-IDRI is a web-accessible database for development and evaluation of CAD systems, all nodule annotations are publicly available. This is not a common setup for challenges. Typically, an independent test set is provided and predictions on this test set are evaluated, but the reference annotations for the test set are not made public. The setup of LUNA16 introduces the risk of biased results. Teams could tune the parameters of their algorithm to show good performance on this particular data set, although the fact that we use such a large set of scans from many different sources somewhat mitigates this risk. We instructed participants that did not have their own training data, to train their system in a particular cross-validation approach. This introduces some risks of making errors, as it is easy to make a mistake in carrying out a cross-validation experiment that goes unnoticed. In fact one team that originally participated in the challenge and reported excellent results had to withdraw because of a bug in the reinitialization of the network weights when starting training for the next fold in cross-validation. Unintended mistakes aside, allowing a cross-validation training procedure means that the presented systems are evaluated on test data while having been trained with data from the same source (institution, scanner, protocol). This may introduce a positive bias in the reported results. This bias is however also present in most systems from the literature.

A future challenge on this topic could incorporate a larger data set and split the data set into training data set with annotations and a dedicated test set for evaluation for which the reference standard is kept secret. This still introduces a risk that teams can visually inspect the test data and the output of their system, notice false positives and false negatives and use that information to improve their performance. This could be circumvented by letting teams upload their algorithms, e.g. as machine executables or software containers.



(a) true positives with highest probability

(b) random true positives at 1 FP/scan

(c) false positives accepted as nodules by radiologists

(d) random false positives at 1 FP/scan

(e) false negatives from the candidate detectors

(f) random false negatives at 1 FP/scan

Figure 2: Examples of true positives, false positives, and false negatives from the combined system. Each lesion is located at the center of the 50×50 mm patch in axial, coronal, and sagittal views.

7. Conclusions

We have presented a web-based framework for a fair and automated evaluation of nodule detection algorithms, using the largest publicly available data set of chest CT scans in which nodule have been annotated by multiple exert human readers. We have shown that combining classical candidate detection algorithms, and analysis of these candidates with convolutional networks yields excellent results. Finally, we have provided an update to the LIDC-IDRI reference standard that includes additional nodules found by CAD. The LUNA16 challenge will remain open for new submissions and can therefore be used as a benchmarking framework for future CT nodule CAD development.

Acknowledgements

The authors acknowledge the National Cancer Institute and the Foundation for the National Institutes of Health, and their critical role in the creation of the free publicly available LIDC-IDRI Database used in this study. This project was funded by a research grant from the Netherlands Organization for Scientific Research, Project No. 639.023.207. ETROCAD team would like to acknowledge the funding agency of Alexander A. Sóñora, the Belgian Development Cooperation, through the VLIR-UOS program with Universidad de Oriente in Santiago de Cuba.

Table 4: Performance summary of published CAD systems evaluated using LIDC-IDRI data set. Different subsets of scans from LIDC-IDRI data set were used by different research groups. For completeness, number of scans, reference standard criteria, and resulting number of nodules used for evaluation are included in the table. The reported performance at one or two operating points is provided.

CAD systems	Year	# scans	slice thickness	nodules size (mm)	agree-ment levels	# nodules	sensitivity (%) / FPs/scan	
Combined LUNA16	-	888	≤2.5	≥3	at least 3	1,186	98.2 / 4.0	96.9 / 1.0
Dou et al. (2016)	2016	888	≤2.5	≥3	at least 3	1,186	90.7 / 4.0	84.8 / 1.0
Setio et al. (2016)	2016	888	≤2.5	≥3	at least 3	1,186	90.1 / 4.0	85.4 / 1.0
Bergtholdt et al. (2016)	2016	243	-	≥3	at least 1	690	85.9 / 2.5	-
Torres et al. (2015)	2015	949	-	≥3	at least 2	1,749	80.0 / 8.0	-
van Ginneken et al. (2015)	2015	865	≤2.5	≥3	at least 3	1,147	76.0 / 4.0	73.0 / 1.0
Brown et al. (2014)	2014	108	0.5-3	≥4	at least 3	68	75.0 / 2.0	-
Choi and Choi (2013)	2013	58	0.5-3	3-30	at least 1	151	95.3 / 2.3	-
Tan et al. (2013)	2013	360	-	≥3	at least 4	-	83.0 / 4.0	-
Teramoto and Fujita (2013)	2013	84	0.5-3	5-20	at least 1	103	80.0 / 4.2	-
Cascio et al. (2012)	2012	84	1.25-3	≥3	at least 1	148	97.0 / 6.1	88.0 / 2.5
Guo and Li (2012)	2012	85	1.25-3	≥3	at least 3	111	80.0 / 7.4	75.0 / 2.8
Camarlinghi et al. (2011)	2011	69	0.5-2	>3	at least 2	114	80.0 / 3.0	-
Riccardi et al. (2011)	2011	154	0.5-3	≥3	at least 4	117	71.0 / 6.5	60.0 / 2.5
Tan et al. (2011)	2011	125	0.75-3	≥3	at least 4	80	87.5 / 4.0	-
Messay et al. (2010)	2010	84	1.3-3	≥3	at least 1	143	82.7 / 3.0	-

References

Aberle, D.R., Adams, A.M., Berg, C.D., Black, W.C., Clapp, J.D., Fagerstrom, R.M., Gareen, I.F., Gatsonis, C., Marcus, P.M., Sicks, J.D., 2011. Reduced lung-cancer mortality with low-dose computed tomographic screening. New England Journal of Medicine 365, 395–409.

American Cancer Society, 2016. Cancer facts and figures 2016.

Armato, S.G., McLennan, G., Bidaut, L., McNitt-Gray, M.F., Meyer, C.R., Reeves, A.P., Zhao, B., Aberle, D.R., Henschke, C.I., Hoffman, E.A., Kazerooni, E.A., MacMahon, H., Beek, E.J.R.V., Yankelevitz, D., Biancardi, A.M., Bland, P.H., Brown, M.S., Engelmann, R.M., Laderach, G.E., Max, D., Pais, R.C., Qing, D.P.Y., Roberts, R.Y., Smith, A.R., Starkey, A., Batrah, P., Caligiuri, P., Farooqi, A., Gladish, G.W., Jude, C.M., Munden, R.F., Petkovska, I., Quint, L.E., Schwartz, L.H., Sundaram, B., Dodd, L.E., Fenimore, C., Gur, D., Petrick, N., Freymann, J., Kirby, J., Hughes, B., Casteele, A.V., Gupte, S., Sallamm, M., Heath, M.D., Kuhn, M.H., Dharaiya, E., Burns, R., Fryd, D.S., Salganicoff, M., Anand, V., Shreter, U., Vastagh, S., Croft, B.Y., 2011. The lung image database consortium (LIDC) and image database resource initiative (IDRI): a completed reference database of lung nodules on CT scans. Medical Physics 38, 915–931.

Armato, S.G., Roberts, R.Y., Kocherginsky, M., Aberle, D.R., Kazerooni, E.A., Macmahon, H., van Beek, E.J.R., Yankelevitz, D., McLennan, G., McNitt-Gray, M.F., Meyer, C.R., Reeves, A.P., P.Caligiuri, Quint, L.E., Sundaram, B., Croft, B.Y., Clarke, L.P., 2009. Assessment of radiologist performance in the detection of lung nodules: dependence on the definition of “truth”. Academic Radiology 16, 28–38.

Armato III, S.G., McLennan, G., Bidaut, L., McNitt-Gray, M.F., Meyer, C.R., Reeves, A.P., Zhao, B., Aberle, D.R., Henschke, C.I., Hoffman, E.A., Kazerooni, E.A., MacMahon, H., van Beek, E.J., Yankelevitz, D., Biancardi, A.M., Bland, P.H., Brown, M.S., Engelmann, R.M., Laderach, G.E., Max, D., Pais, R.C., Qing, D.P., Roberts, R.Y., Smith, A.R., Starkey, A., Batra, P., Caligiuri, P., Farooqi, A., Gladish, G.W., Jude, C.M., Munden, R.F., Petkovska, I., Quint, L.E., Schwartz, L.H., Sundaram, B., Dodd, L.E., Fenimore, C., Gur, D., Petrick, N., Freymann, J., Kirby, J., Hughes, B., Casteele, A.V., Gupte, S., Sallam, M., Heath, M.D., Kuhn, M.H., Dharaiya, E., Burns, R., Fryd, D.S., Salganicoff, M., Anand, V., Shreter, U., Vastagh, S., Croft, B.Y., Clarke, L.P., 2015. Data from LIDC-IDRI.

Bastien, F., Lamblin, P., Pascanu, R., Bergstra, J., Goodfellow, I., Bergeron, A., Bouchard, N., Warde-Farley, D., Bengio, Y., 2012. Theano: new features and speed improvements. arXiv preprint .

Bergtholdt, M., Wiemker, R., Klinder, T., 2016. Pulmonary nodule detection using a cascaded SVM classifier, in: Medical Imaging, International Society for Optics and Photonics. pp. 978513–978513.

Brown, M.S., Lo, P., Goldin, J.G., Barnoy, E., Kim, G.H.J., McNitt-Gray, M.F., Aberle, D.R., 2014. Toward clinically usable CAD for lung cancer screening with computed tomography. European Radiology .

Camarlinghi, N., Gori, I., Retico, A., Bellotti, R., Bosco, P., Cerello, P., Gargano, G., Torres, E.L., Megna, R., Peccarisi, M., Fantacci, M.E., 2011. Combination of computer-aided detection algorithms for automatic lung nodule identification. International Journal of Computer Assisted Radiology and Surgery .

Cascio, D., Magro, R., Fauci, F., Iacomi, M., Raso, G., 2012. Automatic detection of lung nodules in CT datasets based on stable 3D mass-spring models. Computers in Biology and Medicine .

Cerello, P., Cheran, S.C., Bagnasco, S., Bellotti, R., Bolanos, L., Catanzariti, E., De Nunzio, G., Fantacci, M.E., Fiorina, E., Gargano, G., et al., 2010. 3-d object segmentation using ant colonies. Pattern Recognition 43, 1476–1490.

Chialvo, D.R., Millonas, M.M., 1995. How swarms build cognitive maps, in: The biology and technology of intelligent autonomous agents. Springer, pp. 439–450.

Choi, W.J., Choi, T.S., 2013. Automated pulmonary nodule detection system in computed tomography images: A hierarchical block classification approach. Entropy 15, 507–523.

Clark, K., Vendt, B., Smith, K., Freymann, J., Kirby, J., Koppel, P., Moore, S., Phillips, S., Maffitt, D., Pringle, M., Tarbox, L., Prior, F., 2013. The cancer imaging archive (TCIA): Maintaining and operating a public information repository. Journal of Digital Imaging 26, 1045–1057.

Dieleman, S., Schlüter, J., Raffel, C., Olson, E., Sønderby, S.K., Nouri, D., Maturana, D., Thoma, M., Battenberg, E., Kelly, J., et al., 2015. Lasagne: First release. Zenodo: Geneva, Switzerland .

Dietterich, T.G., 2000. Ensemble methods in machine learning, in: Multiple Classifier Systems. Springer Science Heidelberg, pp. 1–15.

Dou, Q., Chen, H., Yu, L., Qin, J., Heng, P.A., 2016. Multi-level contextual 3D CNNs for false positive reduction in pulmonary nodule detection. IEEE Transactions on Biomedical Engineering , 1–1.

Efron, B., Tibshirani, R.J., 1994. An introduction to the bootstrap. volume 57. CRC press.

Firmino, M., Morais, A.H., Mendona, R.M., Dantas, M.R., Hekis, H.R., Valentim, R.A., 2014. Computer-aided detection system for lung cancer in computed tomography scans: Review and future prospects. Biomedical Engineering Online 13, 41.

van Ginneken, B., Armato, S.G., de Hoop, B., van de Vorst, S., Duindam, T., Niemeijer, M., Murphy, K., Schilham, A.M.R., Retico, A., Fantacci, M.E., Camarlinghi, N., Bagagli, F., Gori, I., Hara, T., Fujita, H., Gargano, G., Belloti, R., Carlo, F.D., Megna, R., Tangaro, S., Bolanos, L., Cerello, P., Cheran, S.C., Torres, E.L., Prokop, M., 2010. Comparing and combining algorithms for computer-aided detection of pulmonary nodules in computed tomography scans: the ANODE09 study. Medical Image Analysis 14, 707–722.

van Ginneken, B., Setio, A.A.A., Jacobs, C., Ciompi, F., 2015. Off-the-shelf convolutional neural network features for pulmonary nodule detection in computed tomography scans, in: IEEE International Symposium on Biomedical Imaging, pp. 286–289.

Glorot, X., Bengio, Y., 2010. Understanding the difficulty of training deep feedforward neural networks., in: Aistats, pp. 249–256.

Golosio, B., Masala, G.L., Piccioli, A., Oliva, P., Carpinelli, M., Cataldo, R., Cerello, P., De Carlo, F., Falaschi, F., Fantacci, M.E., Gargano, G., Kasae, P., Torsello, M., 2009. A novel multithreshold method for nodule detection in lung CT. Medical Physics 36, 3607–3618.

Guo, W., Li, Q., 2012. High performance lung nodule detection schemes in CT using local and global information. Medical Physics 39, 5157–5168.

He, K., Zhang, X., Ren, S., Sun, J., 2015a. Deep residual learning for image recognition. arXiv:1512.03385 .

He, K., Zhang, X., Ren, S., Sun, J., 2015b. Delving deep into rectifiers: Surpassing human-level performance on imagenet classification, in: Proceedings of the IEEE International Conference on Computer Vision, pp. 1026–1034.

Henschke, C.I., Yankelevitz, D.F., Mirtcheva, R., McGuinness, G., McCauley, D., Miettinen, O.S., 2002. CT screening for lung cancer: Frequency and significance of part-solid and nonsolid nodules. American Journal of Roentgenology 178, 1053–1057.

Hinton, G.E., Srivastava, N., Krizhevsky, A., Sutskever, I., Salakhutdinov, R.R., 2012. Improving neural networks by preventing coadaptation of feature detectors. arXiv preprint .

International Commission on Radiation Units and Measurements, 2008. Receiver operating characteristic analysis in medical imaging. Journal of the ICRU 8, 1–62.

Jacobs, C., van Rikxoort, E.M., Twellmann, T., Scholten, E.T., de Jong, P.A., Kuhnigk, J.M., Oudkerk, M., de Koning, H.J., Prokop, M., Schaefer-Prokop, C., van Ginneken, B., 2014. Automatic detection of subsolid pulmonary nodules in thoracic computed tomography images. Medical Image Analysis 18, 374–384.

Jacobs, C., van Rikxoort, E.M., Murphy, K., Prokop, M., Schaefer-Prokop, C.M., van Ginneken, B., 2016. Computer-aided detection of pulmonary nodules: a comparative study using the public LIDC/IDRI database. European Radiology .

Karpathy, A., Toderici, G., Shetty, S., Leung, T., Sukthankar, R., Fei-Fei, L., 2014. Large-scale video classification with convolutional neural networks, in: Computer Vision and Pattern Recognition (CVPR), 2014 IEEE Conference on, IEEE. pp. 1725–1732.

Kazerooni, E.A., Austin, J.H., Black, W.C., Dyer, D.S., Hazelton, T.R., Leung, A.N., McNitt-Gray, M.F., Munden, R.F., Pipavath, S., 2014. ACR–STR practice parameter for the performance and reporting of lung cancer screening thoracic computed tomography (CT). Journal of Thoracic Imaging 29, 310–316.

Kuhnigk, J.M., Dicken, V., Bornemann, L., Bakai, A., Wormanns, D., Krass, S., Peitgen, H.O., 2006. Morphological segmentation and partial volume analysis for volumetry of solid pulmonary lesions in thoracic CT scans. IEEE Transactions on Medical Imaging 25, 417–434.

Li, Q., Arimura, H., Doi, K., 2004. Selective enhancement filters for lung nodules, intracranial aneurysms, and breast microcalcifications, in: International Congress Series, Elsevier. pp. 929–934.

Li, Q., Sone, S., Doi, K., 2003. Selective enhancement filters for nodules, vessels, and airway walls in two- and three-dimensional CT scans. Medical Physics 30, 2040–2051.

Manos, D., Seely, J.M., Taylor, J., Borgaonkar, J., Roberts, H.C., Mayo, J.R., 2014. The lung reporting and data system (lu-rads): a proposal for computed tomography screening. Canadian Association of Radiologists Journal 65, 121–134.

Messay, T., Hardie, R.C., Rogers, S.K., 2010. A new computationally efficient CAD system for pulmonary nodule detection in CT imagery. Medical Image Analysis 14, 390–406.

Murphy, K., van Ginneken, B., Schilham, A.M.R., de Hoop, B.J., Gietema, H.A., Prokop, M., 2009. A large scale evaluation of automatic pulmonary nodule detection in chest CT using local image features and k-nearest-neighbour classification. Medical Image Analysis 13, 757–770.

Naidich, D.P., Bankier, A.A., MacMahon, H., Schaefer-Prokop, C.M., Pistolesi, M., Goo, J.M., Macchiarini, P., Crapo, J.D., Herold, C.J., Austin, J.H., Travis, W.D., 2013. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the fleischner society. Radiology 266, 304–317.

Niemeijer, M., Loog, M., Abràmoff, M.D., Viergever, M.A., Prokop, M., van Ginneken, B., 2011. On combining computer-aided detection systems. IEEE Transactions on Medical Imaging 30, 215–223.

Prasoon, A., Petersen, K., Igel, C., Lauze, F., Dam, E., Nielsen, M., 2013. Deep feature learning for knee cartilage segmentation using a triplanar convolutional neural network, in: Medical Image Computing and Computer-Assisted Intervention–MICCAI 2013, Springer. pp. 246–253.

Retico, A., Delogu, P., Fantacci, M.E., Gori, I., Martinez, A.P., 2008. Lung nodule detection in low-dose and thin-slice computed tomography. Computers in Biology and Medicine 38, 525–534.

Retico, A., Fantacci, M.E., Gori, I., Kasae, P., Golosio, B., Piccioli, A., Cerello, P., De Nunzio, G., Tangaro, S., 2009. Pleural nodule identification in low-dose and thin-slice lung computed tomography. Computers in Biology and Medicine 39, 1137–1144.

Riccardi, A., Petkov, T.S., Ferri, G., Masotti, M., Campanini, R., 2011. Computer-aided detection of lung nodules via 3D fast radial transform, scale space representation, and Zernike MIP classification. Medical Physics 38, 1962–1971.

van Rikxoort, E.M., de Hoop, B., Viergever, M.A., Prokop, M., van Ginneken, B., 2009. Automatic lung segmentation from thoracic computed tomography scans using a hybrid approach with error detection. Medical Physics 36, 2934–2947.

Ronneberger, O., Fischer, P., Brox, T., 2015. U-net: Convolutional networks for biomedical image segmentation. arXiv:150504597 .

Setio, A.A.A., Ciompi, F., Litjens, G., Gerke, P., Jacobs, C., van Riel, S., Wille, M.W., Naqibullah, M., Sanchez, C., van Ginneken, B., 2016. Pulmonary nodule detection in CT images: false positive reduction using multi-view convolutional networks. IEEE Transactions on Medical Imaging .

Setio, A.A.A., Jacobs, C., Gelderblom, J., van Ginneken, B., 2015. Automatic detection of large pulmonary solid nodules in thoracic CT images. Medical Physics 42, 5642–5653.

Sutskever, I., Martens, J., Dahl, G., Hinton, G., 2013. On the importance of initialization and momentum in deep learning, in: Proceedings of the 30th international conference on machine learning (ICML-13), pp. 1139–1147.

Szegedy, C., Liu, W., Jia, Y., Sermanet, P., Reed, S., Anguelov, D., Erhan, D., Vanhoucke, V., Rabinovich, A., 2014. Going deeper with convolutions. arXiv:14094842v1 .

Tan, M., Deklerck, R., Cornelis, J., Jansen, B., 2013. Phased searching with neat in a time-scaled framework: Experiments on a computer-aided detection system for lung nodules. Artificial Intelligence in Medicine .

Tan, M., Deklerck, R., Jansen, B., Bister, M., Cornelis, J., 2011. A novel computer-aided lung nodule detection system for CT images. Medical Physics 38, 5630–5645.

Teramoto, A., Fujita, H., 2013. Fast lung nodule detection in chest CT images using cylindrical nodule-enhancement filter. International Journal of Computer Assisted Radiology and Surgery , 1–13.

Tieleman, T., Hinton, G., 2012. Lecture 6.5-rmsprop: Divide the gradient by a running average of its recent magnitude. COURSERA: Neural Networks for Machine Learning 4.

Torres, E.L., Fiorina, E., Pennazio, F., Peroni, C., Saletta, M., Camarlinghi, N., Fantacci, M.E., Cerello, P., 2015. Large scale validation of the M5L lung CAD on heterogeneous CT datasets. Medical Physics 42, 1477–1489.

Wen, Y., Zhang, K., Li, Z., Qiao, Y., 2016. A discriminative feature learning approach for deep face recognition, in: European Conference on Computer Vision, Springer. pp. 499–515.

Xu, K., Ba, J., Kiros, R., Cho, K., Courville, A., Salakhutdinov, R., Zemel, R.S., Bengio, Y., 2015. Show, attend and tell: Neural image caption generation with visual attention. arXiv preprint 2, 5.

Zagoruyko, S., Komodakis, N., 2016. Wide residual networks. arXiv preprint .