RRc-UNet 3D for lung tumor segmentation from CT scans of Non-Small Cell Lung Cancer patients

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Abstract

Lung cancer is a grave disease that accounts for more than one million deaths, and Non-Small Cell Lung Cancer (NSCLC) accounts for 85\% of all lung cancers. Rapid detection of lung cancer could reduce the mortality rate and increase the patient’s survival rate, in which tumor segmentation plays a significant role in the diagnosis and treatment of lung cancer. Nevertheless, manual segmentation by radiologists can be time-consuming and labor-intensive. In recent years, deep learning methods have achieved good results in medical image segmentation. In this paper, RRc-UNet 3D, a variant of the U-Net model, was proposed to perform tumor segmentation in Computed Tomography (CT) images of NSCLC patients. This network was trained end-to-end from a small set of CT scans of NSCLC patients, then the trained model was validated on another set of CT scans of NSCLC patients. The experimental results showed that our model can provide a highly accurate segmentation of tumors in the 3D volume of CT images.

1. Introduction

Lung cancer is the second most common cancer worldwide with more than 230,000 new cases annually. Early detection of lung cancer is critical to saving patients. A lung tumor refers to a small and visible lesion in the lung. Tumor segmentation plays a vital role in the used diagnosis and aggressive treatment of lung cancer. It can help the diagnosis of radiologists and help train new radiologists. In most modalities to acquire the image of the cancer patient, Computed Tomography (CT) is an effective medical screening that can be used for the diagnosis and detection of lung cancer. As CT procedures represent a large volume of CT scans with millions of voxels, manual diagnosis and realization of lung diseases are challenging and time-consuming even for experienced radiologists. Thus, automatic computer-aided diagnosis (CAD) for lung CT is a powerful solution to help radiologists. As usual, CAD involves several steps, of which accurate segmentation of tumors is the first step toward the success of the entire CAD system. Although many studies have been conducted, this problem remains a challenge for experts experienced for decades. Since manual segmentation is time-consuming and labor-intensive, an automatic method for nodule segmentation is highly desirable.

Over the past decade, deep learning methods have been at the forefront of computer vision, such as image classification, segmentation, and object detection with several proposed Deep Convolutional Neural Network (DCNN)\cite{1, 2, 3, 4, 5, 6, 7}. The methods most often focus on image classification tasks on very large-scale datasets like ImageNet\cite{4}, where the outputs are single labels or probability values for each input. Usually, the model consists of some convolutional layers with activation functions followed by down-sampling layers, which reduce the dimensions of the feature maps. As an input traverse through the layers of the network, the number of feature maps increases, but the dimensions of feature maps decrease. Eventually, an activation function (e.g., Sigmoid or Softmax) is applied at the end of the model to compute the probability of the target classes.

Besides classification, segmentation is another success story of deep learning methods in computer vision. A
limited number of classification architectures can be transformed and used for the segmentation tasks. For example, a Fully Convolutional Network (FCN)[6] replaces the last fully connected layer in the neural network with a convolutional layer, which improves the efficiency of segmentation. However, that transformation is not enough, thus the model should be particular with specific operations to provide a better feature map for the segmentation task. In the last years, UNet architecture [7] was a good model that succeeded in segmenting the medical image. Principally, the UNet model [7] consists of two paths: a contracting and an expansive path. The contracting is like a classic CNN to learn from low-level features to the high-level of an input representation. On another side, the expansive consists of an up-sampling of the feature map followed by up-convolution and convolution layers to rebuild the feature at different scaled inputs. A concatenation is made between the convolution layer in the contracting and the up-convolution of the expansive path to get better precise locations. At the final layer of the expansive, a convolution layer is used to map the features to the desired number of classes. This model opened a new benchmark in the segmentation domain by introducing an encoder-decoder (contracting-expansive) architecture. This model bested all previous state-of-the-art segmentation techniques based on CNN and pixel-wise classification.

Generally, the model for segmentation tasks like the UNet model requires both convolutional encoding and decoding paths. The encoding encodes the input image into a large number of feature maps with small dimensions. The decoding path performs up-convolution operations to produce segmentation maps with the same dimension as the original input image. Therefore, the architecture model for the segmentation task has double the number of parameters compared to the classification model. Thus, it is interesting to design the model for segmentation tasks that can ensure performance with a small number of parameters.

In this work, we introduce another 3D architecture that inspired from UNet [7], Residual Neural Network [3], Recurrent CNN [5] and R2U-net [8], named RRc-UNet 3D, for segmenting lung tumor from 3D volume of CT image of a NSCLC patients. Our model has the same structure as U-net [7], but we have modified the core inside each level of the encoder and decoder paths. Our model achieved an accurate segmentation of tumor in CT scans. The highlighted points of our method are summarized as follows:

- The proposed model inputs lung CT volume (3D) and outputs the segmentation of the tumors inside the lung without any post-processing operation.
- The proposed model can provide the results in a short time, e.g., the model provides the predictions of lung tumors for 41 testing patients in less than 3 minutes.
- This prediction can be used to assess the development of the tumor region, as well as diagnosis and treatment of cancer.

This paper is organized as follows: The following section discusses the related works. Section 3 presents the methodology, which details the RRc-UNet 3D architecture and the loss function used to train the model. Section 4 details the experimental process: Firstly, we describe the datasets for the experiment. Secondly, we present the evaluation scores in this study and the model’s implementation. Finally, we show the experimental results. Section 5 points out some concluding remarks from our works.

2. Related Work

Initial approaches for lung/tumor segmentation consider the characteristics of the image or based on the shape knowledge by using the traditional image processing technique such as thresholding based on the grey-level, adaptive thresholding technique, region growing, image registration [9], or the others [10]. However, these methods are computationally expensive, and it is difficult to generalize the learning features.

Among diverse modalities for acquiring medical images, the CT scan is a usual choice of the clinician to work with cancer patients, for example, for lung or liver cancer [11]. In a lung CT scan, it is easy to distinguish the lung parenchyma because this region is large and it takes up most of the space on an image. However, the tumor region is a difficult question when the number of tumor voxels is very tiny compared to the total lung. Therefore, tumor segmentation could be a challenge in many studies about lung diseases [12, 13, 14].

In recent years, Convolutional Neural Networks (CNNs) have been applied to various medical image segmentation tasks and it has achieved numerous success. On lung disease, CNNs models can be used to analyze lung CT scans [15]. Their applications vary from detecting the lung pathology segmentation [15], classifying the lung region [15, 16] to segmenting the lung volume [17]. In the approaches to provide whole volume of lung segmentation, most of applications have chosen to consider independently each slice of CT volume: Ravindra Patil et al. [18] and Brahim A. S. et al. [17] proposed different modifications on UNet model to provide the segmentation of slices in CT volume. Lei Geng et al. [19] presented a combination of VGG-16 [20] and dilated convolution to provide the lung segmentation. Swati P. Pawar et al. [21] have proposed a conditional generative adversarial network to encode the features from the slices of CT image. Then, the encoder and decoder were used to extract the multi-scales features and to give the lung segmentation, respectively. In whole 3D approach, Negahdar et al. [22] have proposed a volumetric segmentation network based on V-net [23] for 3D...
volumetric medical segmentation. Md Zahangir Alom et al. [8] proposed RU-Net and R2U-Net models to provide the segmentation of medical images on several benchmarks.

In the lung tumor segmentation approach, Hongtao Xie et al. [24] have proposed a framework with 2D CNN to assist the CT reading process consisting of two steps: (1) nodule candidature detection based on a Faster R-CNN model integrated a deconvolution layer to enlarge the feature map. They trained the model on the slices of the CT scan, then merged the candidates to obtain the results; (2) false positive reduction based on training a classifier to reduce the false positive produced by the first step. Fuli Zhang et al. [25] have modified ResNet and applied it to segment the gross tumor in the CT scans of NSCLC. Evi Kopelowitz et al. [26] employed a MaskRCNN to handle 3D images to detect and segment lung nodules from CT scans. Uday Kamal et al. [27] proposed a Recurrent 3D-DenseUNet based on a recurrent multiple Convolutional Long Short-Term Memory for lung tumor segmentation.

3. Methodology

In this section, we present the architecture of the proposed model, the RRc-UNet 3D model. Then, we describe the loss functions used to train the model.

3.1. RRcUnet 3D architecture

Figure 1 shows the structure of the RRc-UNet 3D. Depending on the requirements of the applications, the depth and layers at each model’s level are different. After testing different values for the depth of the model, we have decided to use five levels for the proposed model. In addition, we made some modifications to the structure of the model to adapt to our problem: (1) the layers have been changed to adapt with 3D input features; (2) each level of contracting and the expansive path contains a Residual Recurrent block (RRc); (3) the layers in each RRc block have been re-organized to adapt with our question; (4) the number of channels of the input is doubled before reducing the space to the next level.

Figure 2 illustrates the structure of a RRc block consisting of two Recurrent Blocks (RBs). The input traverses a 3D Convolutional layer. Then, the convoluted features will be fed to the RBs. Finally, it is concatenated to the output of RBs for providing the outcome of the RRc block. In our design, a RB is a repetition of t times (e.g., t = 2) of a group including three consecutive layers: Convolutional 3D layer, Group Normalization (GN) [28], and PreLU activation [2] function. Firstly, the GN is used instead of Batch normalization (BN) [39] because BN increases the error rapidly caused by inaccurate batch statistics estimation when using a small batch. On the opposite, GN divides the channels into groups and computes the mean and variance for normalization within each group. GN’s computation is independent of batch sizes, and its accuracy is stable in a wide range of batch sizes. Second, the PreLU activation function [2] is used instead of the ReLU activation function [30] to make the leakage coefficient a parameter learned along with the other network parameters. Really, RB takes full advantage of the spatial continuity of the slices in the volume.
number of feature channels, a concatenation with the corresponding cropped feature map from the contracting, followed by a RRc block to provide the information context of the feature map and a Dropout layer. Finally, a $1 \times 1$ Convolution layer maps the feature to the number of classes. In this work, we trained the model to classify the voxels into three categories: background, lung parenchyma, and tumor. However, the main goal is to provide the segmentation of tumors. The output of the lung parenchyma map is to improve the segmentation of lung parenchyma from the previous step in our application.

Table 1 details the input/output images at each level of the RRc-U-Net 3D model. The input is a two-channel image consisting of a CT scan and lung parenchyma segmentation. In the encoding path, we decrease the dimensions of the images and increase the number of channels after each level; in the decoder path, we reduce the number of channels but increase the dimensions of the images.

There are several advantages of the proposed model compared to U-Net based on the comparison of network parameters. The proposed model with two folds ($t=2$) in Recurrent Block has the same parameters as the U-Net model but shows better performance on the segmentation tasks.

### 3.2. Loss function

The main objective of RRc-U-Net 3D is to provide the segmentation of tumors, while it predicts the pixels into three categories: background, lung parenchyma, and tumor region. Thus, the tumor region is a tiny part compared to the background region and lung parenchyma; therefore, it is difficult to extract the features of tumor regions, which reduces the confidence of the model. So, the tumor regions are considered difficult samples. The background and lung parenchyma are large regions, it is easier to extract these regions than the tumor ones. These samples are seen as easy samples. To increase the model’s confidence, we have to remark on this point while training the model. Therefore, the Focal loss (FL) \((\text{Eq. 32})\), expressed in Equation 1, can be used to solve this concern. It down-weights the contribution of easy samples and enables the model to focus more on learning difficult samples. In addition, Focal loss works well for highly imbalanced class scenarios.

\[
FL(p_t) = -\alpha_t (1 - p_t) \gamma \log(p_t)
\]

Here, $\gamma > 0$ and $\alpha$ generally range from $[0, 1]$. When $\gamma = 1$, Focal loss become Cross-entropy loss \([33]\). $p_t$ is the model’s estimated probability, $\alpha$ is used to adjust the distribution of the easy sample, and $(1 - p_t)^\gamma$ is a dynamic scaling factor to adjust the distribution of hard samples. In our implementation, we have set $\gamma = 2$ and $\alpha = 1$, but they can be treated as hyper-parameters.

As usual, Dice loss (DL) \([23]\), expressed in Equation 2, is usually used for the segmentation problems in deep learning.

\[
DL = \frac{1}{N} (1 - DSC)
\]

Where, $N$ is the number of samples, $DSC$ is dice coefficient expressed by Equation 5.

According to Dice loss, it considers only the segmented objective regions to be sure that the model focuses more on extracting the tumor regions than the others. Following that, the other regions (healthy regions) are ignored. However, it is unreasonable to ignore healthy regions, which also contain important information, e.g., the features of lung parenchyma. If the model can compare the features from objective regions and healthy regions, the performance of the model can be enhanced. To solve this problem, the Generalized Dice loss (GDL) \([34]\) is a good candidate. It is the multi-class extension of Dice loss where the weight of each class is inversely proportional to the square of label frequencies \((\text{Eq. 3})\).

\[
GDL = 1 - \frac{2|W(2\tilde{Y} - 1) \cap W(2Y - 1)|}{|W(2\tilde{Y} - 1)| + |W(2Y - 1)|}
\]

Where, $W$, $Y$, and $\tilde{Y}$ are the weights generated according to the segmentation labels, ground truth, and predicted segmentation, respectively.

Thus, our application meets both of the two mentioned problems. Therefore, we have combined the two losses for training the model \((\text{Eq. 4})\).

\[
Loss = Focal Loss + G.Dice Loss
\]

### 4. Experiments and Results

#### 4.1. Dataset and Pre-processing

RRc-U-Net 3D was trained and validated on 3D CT scans of NSCLC patients. Images were collected from 2 sources: the public and local datasets. The public dataset consists of 494 CT scans from 3 public datasets: NSCLC-Radiomics-Interobserver1 dataset \([35]\), NSCLC-Radiomics-Genomics dataset \([36]\) and LungDecath dataset \([37]\). The local dataset consists of 41 CT scans of local NSCLC patients. Each image has a variable size from $(512 \times 512 \times 60)$ to $(512 \times 512 \times 600)$ pixels. All images were reformatted from standard DICOM to Neuroimaging Informatics Technology Initiative (NIfTI) format created by the National Institutes of Health \([38]\). The NIfTI file held the 3D image matrix and diverse metadata. Figure 3 shows a 3D image for volumetric measurements of lung parenchyma across three axes.

#### Data splitting and pre-processing:

The images from 2 sources were divided into two sets: train/validation and testing sets. The train/validation set
avability within the database. In this work, the input images go through the three following steps for preparing the images:

1. The image intensity of each slice was first truncated in the range of $[-1200, 600]$.

2. Z-normalization was performed on each CT scan.

3. The CT scans were cropped to focus on the lung region and converted to $256 \times 256 \times 48$ pixels.

As mentioned, our model receives an input of two channels which consist of a CT scan and segmentation of lung parenchyma. However, the two datasets: R.Genomics and LungDecath do not provide the ground truth for the lung parenchyma. Thus, we have designed another variant of Unet with helping of the Coordinated Convolutional layer [39] to extract the lung parenchyma in another task [31]. This model has been trained and validated on other datasets. The results showed that it can be used as an extractor to provide the segmentation of lung parenchyma. The outputted segmentation was good enough to be used as ground truth (input) for the task of segmentation of tumors.

### Data augmentation

Due to the limitation of the number of samples in the training set, some augmentation operations have randomly been applied to the image during the training process, for example, flipping, deformation, and affine transformation. Figure 4 shows an augmented example in our dataset.

#### 4.2. Implementation details

The model was implemented using the PyTorch library [40]. Models were trained in 1000 epochs using an Adam optimization [41] with a weight decay of $10^{-4}$. The learning rate was set to $3 \times 10^{-4}$, batch size was equal to 1, and the loss was backward after obtaining forward values of all patients. An early stopping strategy was applied by monitoring the validation loss to prevent over-fitting.
4.3. Evaluation metrics

The evaluation of 3D lung parenchyma segmentation is based on comparing ground truth and outputted segmentation from the model. For quantitative analysis of the predicted segmentation, several performance metrics are considered, including the Dice score coefficient (DSC), Jaccard similarity (IOU), and F1 score [42].

DSC is expressed as in Eq. 5, the IOU score is represented using Eq. 6 according to [43] and [44], respectively. Here, GT and SP refer to the ground truth and predicted segmentation, respectively.

\[ DSC = \frac{2(|GT \cap SP|)}{|GT| + |SP|} \] (5)

\[ IOU = \frac{|GT \cap SP|}{|GT \cup SP|} \] (6)

Furthermore, F1 is calculated by using the Eq. 7.

\[ F1 = \frac{2 \cdot (\text{precision} \times \text{recall})}{\text{precision} + \text{recall}} = \frac{2TP}{2TP + FP + FN} \] (7)

where True Positive (TP), False Positive (FP) and False Negative (FN) are the variables.

4.4. Results and Analysis

As mentioned, we trained the RRc-UNet 3D model to classify the voxels into three categories: background, lung parenchyma, and tumor; but the main objective was to segment the tumor regions. To evaluate the model’s performance, we computed the scores on three labels and only on tumor label. Table 3 and 4 show the evaluation scores on three categories and tumor only, respectively.

<table>
<thead>
<tr>
<th>Score</th>
<th>Dice coeff.</th>
<th>IOU</th>
<th>F1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>0.863</td>
<td>0.9971</td>
<td>0.9982</td>
</tr>
</tbody>
</table>

Table 3: The evaluation scores of RRc-UNet 3D on three labels.

These scores showed that the RRc-UNet 3D model highly perform on the validation set to provide the prediction for three categories. It consistently provides high evaluation scores for the three classes. It is evident because the lung parenchyma segmentation has supported it to predict the tumor location. Concerning the tumor region, the model has provided a significant Dice coefficient, even higher than the three categories. On other metrics, we obtained a good score as well, but they are still tiny compared to the performance of the three classes.

The trained model has been used to predict the segmentation for each image in the testing set (local dataset). Then, the predictions were compared with ground truth by calculating the Dice coefficient. It is worth noting that we take into account only the segmentation of the tumor in this step. Finally, the average Dice coefficient has been computed for all testing images. We have obtained an average Dice coefficient of 0.7682 for all 41 CT scans in the testing set. Figures 5 and 6 illustrate the predictions of two samples in the testing set with high and low dice coefficients, respectively. In the first case, the RRc-UNet 3D model provides perfect segmentation of the entire tumor inside the lung. In the second one, the model detects only a limited tumor region, which is big and has spread to the outside of the lung.

To better understand the difference between the results on the two datasets (validation and test), we look at the histogram of the distribution of Dice scores of the patients in
the testing set. Figure 7 illustrates the number of images in a different range of Dice scores. We have 24 well predictions with dice scores greater than 0.8; 6 good predictions with scores from 0.75 to 0.8; 5 cases have scored in the range from 0.5 to 0.75; and 5 cases have dice scores less than 0.5. In summary, we obtain 30 out of 41 CT scans with Dice scores greater than 0.75; 11 CT scans have scores smaller than 0.75.

Thus, our model has worked fine to segment the tumor inside the lung. It provides a perfect segmentation for the small tumor or the tumor located inside the lung. The model meets the difficulties of the large tumor staying at the border of the lung. Figure 8 illustrates a slice of the easy and hard cases in the testing set. Both two tumors are big, the difference is the location of the tumors: the tumor of the hard case mostly stays on the wall of the lung, while the other begins to contact the wall of the lung.

4.5. Comparison with other block concepts

To audit the efficiency of the RRc block, we replaced the RRc block with other concepts. In this work, we investigated the efficiency of the CGPD block, the Residual block, and the Recurrent block. For each concept, we placed two blocks at each level of the model instead of a RRc block. The modified models have been trained in the same scenarios as we have done with the RRc block.

**CGPD block:** consists of a Convolution layer, a Group normalization (GN) layer \([28]\), a PreLU activation function \([2]\), and a Dropout layer \([45]\) (Figure 9). The number of input channels is doubled at the second block before applying a max pooling layer to reduce the spatial size and send it to the next level.

**Residual block:** is constructed from the convolutional layer, group normalization, and PreLU activation as well (Fig. 10). In the Unet model, we placed two Residual blocks followed by two dropout layers.

**Recurrent block:** includes three consecutive layers: Convolutional layer, Group Normalization, and PreLU activation. These layers can repeat in several times (e.g., \(t = 2\)) to provide the output.

Table 5 presents the evaluation scores of the model by using different concepts of blocks. We see that models with different concepts of blocks provide a good score in 3 categories. It is obvious because we have support from the lung parenchyma segmentation to pre-indicate the tumor location. However, we see the difference in the scores that concern the tumor region. The best Dice coefficient is obtained
Figure 9: Layers in a CGPD block

Figure 10: Layers in a Residual block

with the RRc block. The same score on CGPD is also good, but it is very worst on the Residual and Recurrent blocks.

<table>
<thead>
<tr>
<th>Concepts</th>
<th>IOU 3 labels</th>
<th>F1 3 labels</th>
<th>Dice coeff. tumor</th>
<th>IOU tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGPD block</td>
<td>0.9955</td>
<td>0.9974</td>
<td>0.7837</td>
<td>-</td>
</tr>
<tr>
<td>Residual block</td>
<td>0.9955</td>
<td>0.9973</td>
<td>0.1737</td>
<td>0.5843</td>
</tr>
<tr>
<td>Recurrent block</td>
<td>0.9957</td>
<td>0.9973</td>
<td>0.1992</td>
<td>0.5825</td>
</tr>
<tr>
<td>RRc block</td>
<td><strong>0.9971</strong></td>
<td><strong>0.9982</strong></td>
<td><strong>0.8777</strong></td>
<td><strong>0.7274</strong></td>
</tr>
</tbody>
</table>

Table 5: The comparison of the evaluation scores among different concepts of block for Unet model.

It is not clear to compare our results with other results because we are on different approaches [25, 26, 27]. For example, we consider the whole CT scan with the assistance of lung parenchyma segmentation; while Uday Kamal et al. [27] focus only on the local regions (several slices) around the tumors. However, RRc-UNet 3D model can segment tumor regions with very satisfactory performance and have the potential to locate and analyze tumor lesions.

5. Conclusion

In this work, we presented an RRc-UNet 3D model to provide tumor segmentation from CT scans of NSCLC patients. We have obtained an accurate segmentation with a Dice coefficient of 0.8777 for the validation set. The trained model has been used to predict tumor segmentation from the CT scans of a local dataset. The average Dice score on the testing set showed that our model worked fine to provide tumor segmentation (average Dice coefficient on the testing set of 0.7682). We saw also a bias between the Dice scores on the validation and testing set. The problem was found as the difficulties of the big tumors, which stay at the border of the lung. The advantage of the method is the model can work with a whole 3D volume of the CT scan, and it can be applied to a wide area of different medical image segmentation tasks. Another objective is to generalize the approach for use in another work, for example, to automatically prelocate the tumor position. Future work could be focused on considering the two sets of small and big tumors.

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References


