Pyramid Focusing Network for mutation prediction and classification in CT images

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Abstract. Predicting the mutation status of genes in tumors is of great clinical significance. Recent studies have suggested that certain mutations may be noninvasively predicted by studying image features of the tumors from Computed Tomography (CT) data. Currently, this kind of image feature identification method mainly relies on manual processing to extract generalized image features alone or machine processing without considering the morphological differences of the tumor itself, which makes it difficult to achieve further breakthroughs. In this paper, we propose a pyramid focusing network (PFNet) for mutation prediction and classification based on CT images. Firstly, we use Space Pyramid Pooling to collect semantic cues in feature maps from multiple scales according to the observation that the shape and size of the tumors are varied. Secondly, we improve the loss function based on the consideration that the features required for proper mutation detection are often not obvious in cross-sections of tumor edges, which raises more attention to these hard examples in the network. Finally, we devise a training scheme based on data augmentation to enhance the generalization ability of networks. Extensively verified on clinical gastric CT datasets of 20 testing volumes with 63648 CT images, our method achieves the accuracy of 94.90% in predicting the HER-2 genes mutation status of at the CT image.

Keywords: Mutation prediction, Computed Tomography (CT) data, Neural network.

1 Introduction

Understanding the information about genetic mutations hidden in cancer is critical to personalized cancer treatment. Traditionally, mutation sequencing on biopsies has become the gold standard for genetic mutation detection, but this increases the potential risk of cancer metastasis. In addition, due to limitations in tumor sampling, DNA quality, and cost, the applicability of biopsy is difficult to sustain [13, 14, 16]. Encouragingly, recent research shows that features extracted from cancer CT images are related to gene expression patterns [1, 3, 9, 23], which provides new ideas for solving this problem.
The detection of genetic mutation status has stimulated researchers’ intensive interest. The radiomics [4] methods based on feature engineering are typical approaches for genetic mutation detection [12, 16, 21]. However, these methods depend heavily on the handcrafted statistical modeling and can only extract generalized image features which lack specificity to gene mutations. By contrast, advanced artificial intelligence models can overcome these problems through a self-learning strategy such as deep learning methods. The deep convolutional neural network (CNN) [7, 15, 19] based methods have been explored for detecting the mutation status of genes. However, the latest CNN-based methods did not take into account the morphological differences between tumor individuals. As illustrated in Fig. 1, the shape and size of tumor vary greatly across different subjects and time points. The fixed-resolution resampling method is used for the input training CT image, which will undoubtedly lose a lot of image information. In addition, discriminant features needed for proper mutation detection are not obvious in the marginal tumors crosssections (e.g. axial slices in the top and bottom regions of a tumors), which is hard for network to mine hidden information. And there is another fact worth noting, the proportion of patients with non-mutations in reality is larger than that of mutant patients, but all methods have not paid attention to this problem.

Different from the existing methods, in order to solve the above problems, we propose a Pyramid Focusing Network (PFNet). Motivated by Spatial Pyramid Pooling (SPP) in computer vision [5], we argue that, SPP can be used to summarize information from different scales and transform tumor images into fixed-dimensional features. This method also removes the limitation that the traditional deep convolution classification network needs to input a fixed image size. Additionally, to compensate that sample imbalance and pay more attention to the CT images on tumor edges, a novel focal loss [10] is proposed to reshape the standard cross entropy loss and greatly enhance the importance of tumor edge CT images. The novel loss is dynamically scaled by using a tunable factor, which automatically decays to down-weigh the contribution of easy samples during training and mainly focus on hard samples. Finally, we developed a special training strategy and established a practical genetic mutation detection system, which can be extended to more mutation types in the future. The main contributions are summarized as follows:
— We propose a pyramid focusing network to reduce the loss of CT image accuracy and can extract the specific semantics of tumors.
— We design a novel focal loss used in this scenario to identify discriminative features in CT images with less certain classification, and balance the proportion of training sample categories.
— We develop a specific training scheme based on data augmentation to enhance the generalization ability of networks.

The rest of this article is organized as follows. A brief overview of related work in Sect. 2. Details of PFNet and data augmentation-based training strategies are described in Sect. 3. Experiments and analysis are given in Sect. 4. Discussion and conclusions are given in Sect. 5.

2 Related Work

In this section, we review recent advances in CT images-based mutation prediction tasks. With the correlation between CT images and gene mutations identified [1, 3, 9, 23], Shiri et al. [18] used different machine learning methods to develop radiomic models for predicting mutational status of EGFR and KRAS. Specifically, they used wavelet (WAV), Laplacian of Gaussian (LOG) and 64 bin discretization (BIN) to extract image features, and then used ROC and AUC to test the predictive performance of the model. Although this is a good attempt, the manually extracted image features are not only time-consuming and laborious, but can only reflect generalized image features that lack specificity to gene mutation. So more researchers are focusing on advanced artificial intelligence models [7, 11, 15, 19, 22].

Nicolas et al. [15] performed experiments on images of non-small cell lung cancer using a deep CNN network and showed prediction results on 10 types of genes. This method does not make deep exploration on the network model, but proves the effectiveness of CNN in predicting gene mutations. Shuo et al. [19] proposed the use of a pre-trained denseNet network to predict EGFR mutation status in lung adenocarcinoma. However, due to the difference between the source domain (ImageNet) [8] and the target domain (CT images), it is difficult to say that the use of transfer learning can bring substantial effects to the task. They suggested fixing the model's input to a 64 * 64 size, which apparently ignores differences in individual tumors and results in loss of image information. In addition, the problem of difficult to identify tumor edge features has not been solved. Lin et al. [10] and Zhao et al. [22] both use 3D denseNet [2] to extract features, but also fail to consider the two problems mentioned above. In addition, the training of 3D networks requires a huge amount of data, and this condition is often not satisfied in practice. Therefore, it is necessary to design a more ingenious network framework and maximize the use of training data to solve the existing problems.
Fig. 2. Schematic view of our proposed framework.

3 Methodology

Fig. 2 is the schematic view of our proposed framework. Because the amount of data is crucial in the field of deep learning, so our training data has been characteristically augmented without changing the nature of the CT data itself. Due to the use of SPP, our system can take 3 channel CT images of different sizes as input. First, hierarchical features are learned and extracted through consecutive dense blocks. Then, SPP module distills semantic cues from multiple scales. These semantic information are then merged to infer the mutation predictions. At the end of the network, we introduce a novel focal loss to guide the network to selectively search for samples in order to learn more efficiently. In addition, we obtained data with multiple resolution specifications based on data augmentation, and iteratively fed them into the network in order to make the model more robust. In the following, we detail the data enhancement, the design details of PFNet, the focal loss function used, and the training strategy.

3.1 Data Augmentation

During training, validation and testing, a cubic ROI (region of interest) containing the entire tumor is manually selected an our model input. Specifically, the ROI only needs to include the complete tumor region, and does not need to accurately locate the tumor at the center of the ROI. This rule saves heavy manual labor and provides guarantee for feature mining. Then, all the adjacent three CT slices were combined as a three-channel image, and the three channels in each image are reordered to form 6 combinations. We also added 7 types of changes to the CT image, thereby increasing the number of training samples to 48 times without changing the nature of the CT data itself. The specific data augmentation strategies used include: transpose, rotate 90-degree, rotate 180-degree, flip up and down, flip left and right, flip left and right after transpose, and rotate 180-degree after transpose, as shown in Fig. 3. It is worth noting that the use of these strategies can facilitate ignoring the location and shape of tumors during model training and focus more on mining valuable information about gene mutations.
3.2 Pyramid Focusing Network Design

Directly applying vanilla CNN networks to predicting the mutation status of genes in tumors performs poor. There are huge morphological differences among tumors. Therefore, as shown in Fig. 2, we propose the PFNet as a solution framework for mutation detection. Specifically, for the forehead part, we deploy a DenseNet [2] to extract features, but made some modifications. The DenseNet we use contains only two block. The main reason is that we define the mutation status prediction of a gene as a binary classification problem. Based on all our training data, it is recommended to make the network design less complicated to make it has sufficient feature extraction ability and better generalization ability. Utilizing the convolution and pooling layers in DenseNet, we acquire a feature map with a shape of $H*W*212$. $H$ and $W$ depend on the input ROI resolution and not a fixed value, which reflects the morphological differences of different tumors.

Then, we use SPP to extract tumor-specific information from different levels and convert a variable-size feature into a fixed-size output. As shown in Fig. 4, four pyramid levels 1, 2, 3, 4 are used in our approach. After this operation, we concatenate the feature maps from different levels and obtain a fixed-dimensional vector for further process.

Finally, the three fully connected layers (FC) follow the SPP module and output the mutation prediction of the gene through the classification function. The number of FC layers plays a crucial role because it reduces the parameters layer by layer to improve the stability of the model without reducing the performance of the model.
3.3 Focal loss for genetic mutation detection

In general classification models, such as DenseNet used in the forehead of our network, the following binary cross entropy is often used as the loss function:

\[
L(p_t) = \begin{cases} 
  -\log(p_t) & y_t = 1 \\
  -\log(1 - p_t) & y_t = 0 
\end{cases}
\]  

(1)

Where \( t \) is the sample index and \( p_t \) is a predicted score, i.e., \( p_t \in [0,1] \), which indicates that the mutation status of the gene of the t-th 3-channel CT image is predicted as the mutation expression category, and \( y_t \) represents the ground truth. In particular, \( y_t = 1 \) indicates that the t-th CT image really belongs to the mutation expression category, and \( y_t = 0 \) indicates that the gene expression status is non-mutation. By \( \min \sum_{t} L(p_t) \), the network can continuously update parameters to achieve the purpose of learning. However, the task of gene mutation detection has two challenges that make binary cross entropy loss difficult to cope with: the features of tumor edge slices are difficult to identify and the training samples are unbalanced.

In order to solve the above two problems, we introduce a novel focal loss in PFNet to improve the binary cross entropy loss (1),
\[
FL(p_t) = \begin{cases} 
\alpha(1-p_t)^\gamma \log(p_t) & y_t = 1 \\
(1-\alpha)p_t^\gamma \log(1-p_t) & y_t = 0
\end{cases}
\] (2)

where \( p_t \) is the predicted score value, \( \gamma \) is a tunable constant and \( \alpha \) is constant in the range of [0, 1].

In (2), the introduction of hyperparameters \( \alpha \) and \( \gamma \) can effectively solve the above-mentioned problems about hard samples (that are tumor edge slices) and sample imbalances. We analyze its effects on the emphasis of hard samples. First, when \( y_t = 1 \), \( p_t \) of an easy sample is close to 1 and \( (1-p_t)^\gamma \) is even closer to 0 with \( \gamma > 1 \). On the contrary, \( p_t \) of a hard sample is far from 1 and \( (1-p_t)^\gamma \) is much larger than those of easy samples, which implies that the hard sample has much more impact on the loss function. Second, when \( y_t = 0 \), \( p_t \) of an easy sample is close to 0 and \( p_t^\gamma \) is even closer to 0 with \( \gamma > 1 \). On the contrary, \( p_t \) of a hard sample is far from 0 and \( p_t^\gamma \) is much larger than those of easy samples. We can similarly conclude that the network will focus more on samples that are prone to misclassification.

In addition, by selecting \( \alpha > 0.5 \) in (2), the sample of the mutation category (\( y_t = 1 \)) has a larger value of the sample of the non-mutation category (\( y_t = 0 \)). This setting can greatly enhance the impact of mutation category data and fully reduce the imbalance of the sample.

### 3.4 Training scheme based on data augmentation

Usually, the designed network model is pre-trained on a very large data set, such as ImageNet [8], which contains 1.2 million images with 1000 categories, and then the pre-trained model is used as an initialization or fixed feature Extractor to complete tasks of interest. This method, called transfer learning, often leads to performance improvements. However, it is difficult to collect a sufficiently large medical data set for transfer learning. Based on this consideration, we design a competitive training method based on data augmentation.

In the 3.1 module, we have augmented the CT data to 48 times, but in the training we have used the center cropping, and the input ROI is cropped to two types of data with resolutions of 64 * 64 and 100 * 100. Then, these three resolution types of CT images will be used to iteratively optimize the model. As shown in Fig. 5, the data augmentation based training scheme is intuitive in design. First, we fed the 64 * 64 resolution CT images obtained by center cropping into the model, and simultaneously trains several competitors with the same initial configurations. Only the winner model with most accurate can be recorded at the validation point. The winner model whose input are the 100 * 100 size CT images can broadcast its parameters to initialize all competitors in the next competition stage. Similarly, the winner model with an input size of 100 * 100 be fine-tuned by fed the original size ROI images to get our final excellent model.
4 Experiments

4.1 Dataset and Evaluation Metrics

We obtained CT images of 20 cases of gastric cancer with HER-2 [17] mutation information from a grade A class 3 hospital in Shanghai. The ROI was then manually labeled by the two doctors with the CT scan information, and we extracted the ROI through an algorithm for training and testing of the model. The size of the final images are different, ranging from 125 to 191. After we expanded the data by the method introduced in module 3.1, we obtained a total of 63,648 CT images. We used a 3:1 validation method on the training and validation set. There are 12 non-mutation data and 3 mutation category data in the training set, and 3 non-mutation data and 2 mutation type data are set in the test set.

For better model evaluation, both CT image level accuracy (Image Acc) and tumor level accuracy (Tumor Acc) are used. First of all, since the 3 channel CT image is sent to the model, we design an evaluation standard for the CT image, which is the prediction accuracy of the model at the CT image level. In other words, Image ACC represents the image probability that the model correctly predicts for all CT images input. Each test case will get the corresponding Image ACC. The average Image ACC can be obtained from the prediction results of all test cases.

In addition, three thresholds are set in our experiments, which are 50%, 70%, and 90%. When the Image ACC of a test case is higher than a threshold, we believe that the model's prediction at this tumor level is correct under the threshold. Tumor ACC represents the correct probability that the model predicts the test tumor under different thresholds. Obviously, if the model has higher Tumor ACC at higher thresholds, which means it has better performance.

4.2 Implementation Details

Our model is implemented with Pytorch and optimized with the SGD algorithm on a NVIDIA Tesla P100 GPU. CT images are normalized as zero mean and unit variance before training and testing. The specific training method of the model is shown in module 3.4. We used PFNet to pretrain on CT images with the resolution of 64 * 64, resulting in a winner model. Then fine-tuned on the 100 * 100 resolution CT images, and continued to generate the winner model. Finally, the original ROI-CT images is used as input to fine-tune the winner model to produce the final excellent model. We set the batch-size to 64 for the training resolutions of 64 * 64 and 100 * 100, and the learning rate is 0.001. The two resolution models were trained in 25 and 15 epochs, respectively. As for the last round of competitive training with ROI-CT images as input, we set the learning rate to 0.001 and the epoch to 50. In addition, we added a dropout
layer with a parameter loss rate of 0.5 between adjacent fully connected layers, which has the advantage of improving the generalization ability of the network.

4.3 Baseline Prediction Models

We compare PFNet with VGG-19 [20], ResNet-34 [6] and DenseNet [2]. These network models have very powerful feature extraction capabilities. It is worth noting that we only use the first two modules of DenseNet-169. In addition, we also compared the model with MIA-CNN [7], which is an advanced gene mutation prediction model proposed by Hussain et al. MIA-CNN uses multiple instance learning and carefully designs the network structure, and has achieved good performance in predicting 4 types of common mutant genes of clear cell renal cancer. In the experiments, we also compare the use of cross-entropy loss (CE) and focal loss (FL). Moreover, DA and T represent the use of data augmentation techniques and corresponding training strategies.

4.4 Results and Analysis

The comparison results are shown in Table 1. Comparing the two models of VGG-19 and ResNet-34, we can see that DenseNet with two blocks performs better on Image ACC (ave). With the same cross-entropy loss function, we can see that our proposed PFNet improves the Image ACC by 0.05 compared to the MIA-CNN model. In the five cases used for testing, the Image ACC of PFNet with cross-entropy loss is higher than that of MIA-CNN. This implies that our proposed PFNet is more ingenious in model design than MIA-CNN. In addition, when focal loss is added to the proposed PFNet, we can see that the image ACC (ave) improves from 0.819 to 0.850. Obviously, the use of focal loss in the model is beneficial for gene mutation prediction. Our experiments also compared the performance improvements brought by data augmentation and training strategies to verify the importance of each module to our system.

| Method          | Image Acc (cases-5) | Tumor Acc (thresholds) |
|-----------------|---------------------|------------------------|
|                 | a | b | c | d | e | ave | > 50% | > 70% | > 90% |
| ResNet-34       | 0.393 | 0.610 | 0.446 | 0.434 | 0.522 | 0.481 | 0.4 | 0 | 0 |
| VGG-19          | 0.549 | 0.664 | 0.698 | 0.473 | 0.681 | 0.613 | 0.8 | 0 | 0 |
| DenseNet        | 0.655 | 0.724 | 0.670 | 0.454 | 0.677 | 0.636 | 0.8 | 0.2 | 0 |
| MIA-CNN         | 0.834 | 0.729 | 0.779 | 0.587 | 0.831 | 0.752 | 1.0 | 0.8 | 0 |
| PFNet+CE        | 0.874 | 0.773 | 0.829 | 0.706 | 0.903 | 0.819 | 1.0 | 1.0 | 0.2 |
| PFNet+FL        | 0.915 | 0.721 | 0.922 | 0.751 | 0.941 | 0.850 | 1.0 | 1.0 | 0.6 |
| PFNet+FL+DA     | 0.959 | 0.943 | 0.962 | 0.830 | 0.981 | 0.935 | 1.0 | 1.0 | 0.8 |
| PFNet+FL+DA+T   | **0.961** | **0.969** | **0.971** | **0.861** | **0.983** | **0.949** | **1.0** | **1.0** | **0.8** |

Table 1. Comparison between different models on five test cases.
In addition, in order to understand in detail the model's prediction on the tumor edge cross section, we perform additional tests on the case-d with the lowest Image ACC in the five test cases in Table 1. We start from the top and bottom of case-d and follow the strategy of extracting one image every an interval to obtain a total of 20 CT images. As shown in Fig. 6, the detailed prediction results of the three methods of MIA-CNN, PFNet (CE), and PFNet (FL) on these 20 CT images are shown.

As can be seen from Fig. 6, we propose that PFNet (using cross-entropy loss) predicts a total of 10 CT images correctly, which is much higher than the MIA-CNN model predicts that there are 4 CT images correctly. It may be that the PFNet model based on SPP can mine multi-scale semantic cues, thereby reducing the loss of image information. In addition, comparing PFNet using different loss, we find that the use of focal loss enables 14 CT images to be correctly predicted. And the correctly predicted slices are closer to the top and bottom of the tumor, which shows that using focal loss can make the model pay more attention to these hard samples, thereby improving the overall performance.

![Image](image.png)

**Fig.6.** Mutation prediction results of CT images of tumor edges in different models.

### 4.5 Study for Focal Loss

In the above comparative experiments, we have found that the introduction of focal loss helps to optimize the learning process and further improve the model effect. We try setting the parameter $\alpha$ in the focal loss between 0 and 1, and $\gamma$ between 1 and 3. The experimental results are shown in Table 2. The experimental model uses PFNet. It is found from the table that in the task of this experiment, we set $\alpha = 0.55$ and $\gamma$ is designed to 2 to obtain the best performance.

| Parameter- $\alpha$ | Parameter- $\gamma$ | Image ACC(%) |
|---------------------|---------------------|--------------|
| 0.55                | 2                   | 79.1         |

**Table 2.** Setting the appropriate loss weight $\alpha$ and $\gamma$ in the focal loss is important.
5 Conclusion

In this paper, we propose a PFNet for mutation prediction and classification of tumor CT images. Firstly, aiming at the characteristics of tumor CT images we add SPP to the network, which allows tumor CT images of different sizes as input to the frame, and extracts reliable representations for output prediction. In addition, under the adjustment of focal loss, the model will pay more attention to hard samples whose features are difficult to identify, and can balance the sample distribution. Finally, with the data augmentation method we used, a competitive training strategy is designed to enhance the generalization ability of the network. Although our experiments are only validated on a small amount of data, the results still confirm that our method has excellent performance in CT image-based mutation detection tasks. In future research, we will apply our method to predict more genotypes and explore the applicability of the system.

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