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Breast Cancer Histopathological Image Classification with Adversarial Image Synthesis

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Abstract— **Data limitation is one of the major challenges in applying deep learning to medical images. Data augmentation is a critical step to train robust and accurate deep learning models for medical images. In this research, we increase the size of a small dataset by using an Auxiliary Classifier Generative Adversarial Network (ACGAN) which generates realistic images along with their class labels.**

We evaluate the effectiveness of our ACGAN augmentation method by performing breast cancer histopathological image classification with deep convolutional neural network (dCNN) classifiers trained on our enhanced dataset. For our classifier, we use a transfer learning approach where the convolutional features are extracted from a pertained model and subsequently fed into several extreme gradient boosting (XGBoost) classifiers. Our experimental results on Breast Cancer Histopathological (BreakHis) dataset show that ACGAN data augmentation, along with our XGBoost classifier increases the classification accuracy by 9.35% for binary classification (benign vs. malignant) and 8.88% for four-class tumor sub-type classification compared with standard transfer learning approach.

I. Introduction and related work

Breast cancer is one of the most common types of cancer in the world. 1 out of 8 women in the United States (around 12% of the total U.S. population) face it sometime in their lifetimes [1]. Besides typical imaging procedures such as digital mammography, physicians also rely on pathologists to review the histopathological images to confirm the diagnoses. However, this process is often laborious and time-consuming. Therefore, it will be extremely helpful if there is a way to automate breast cancer detection in histopathological images to improve women's health.

Deep learning methods show great promise in solving various image processing tasks such as image recognition [2], object tracking [3] and image segmentation [4]. These afformentioned methods can also be applied quite effectively in the field of medical image analysis [5]. Recently, deep learning researchers have come up with novel ways to analyze breast cancer histopathological images for automated diagnosis and treatment planning. Motlagh et al. [6] develop a deep learning framework to classify different breast cancer types in breast histopathological images. In their study, they use various pre-trained networks such as Inception and ResNet in order to obtain the classification results. Spanhol et al. [7] train a convolutional neural network to extract features and use the extracted features to train a classification network. This new framework achieves higher classification accuracy in breast cancer classification than the previous state-of-the-art. Spanhol et al. also conduct [8] another research in breast histopathological image classification which uses patched-based training where the patches are fused in the final classification step. Wei et al. [9] proposed the treatment of all class and sub-class labels as preliminary information, and the use of a novel CNN model called BiCNN as their main classification network. BiCNN has the ability to learn features and inherent rules based on the dataset. In addition, they used a GoogLeNet pre-trained on ImageNet for transfer learning. Gour et al. [10] propose a 152-layered residual network for the classification of breast histopathological images as either benign or malignant.

A major drawback in deep learning is the fact that deeper neural networks are only robust when trained on large amounts of data. Networks trained on few training images are prone to over-fit, and will not generalize well in testing. [11] This challenge is further exacerbated in the medical field since there are limited subjects for certain disease types, high costs of imaging procedures involved, and patient data privacy issues. Current deep learning methods for breast cancer histopathological image classification also suffer from overfitting in the Breast Cancer Histopathological (BreakHis) [12] dataset since it has few available training images. To tackle this problem, various augmentation methods are developed to increase the number of training data and achieve robust performances on evaluation data. One of the popular augmentation approaches is applying affine transformation (e.g., shear, zoom, reflection and rotation) to existing training images. However, the classifical networks can be easily fooled by adding replicated images. Another augmentation strategy is the use of adversarial learning which creates synthetic histopathological images from random noise. In particular, Generative Adversarial Network (GAN)-based methods produce images with high fidelity by taking the underlying disease distribution into account.

In this research, we use an auxiliary classifier generative adversarial network (ACGAN) to increase the number of training images with corresponding disease labels. We both qualitatively and quantitatively evaluate our proposed methodology by performing breast cancer histopathological image classification with the dCNN classifiers trained on augmented dataset. For our classifier, we use a transfer learning approach [13] in which the convolutional features are first extracted from the pre-trained model and subsequently passed onto the XGBoost classifier. Our proposed method offers a new way to deal with limited training data when applying dCNN classifiers to medical images

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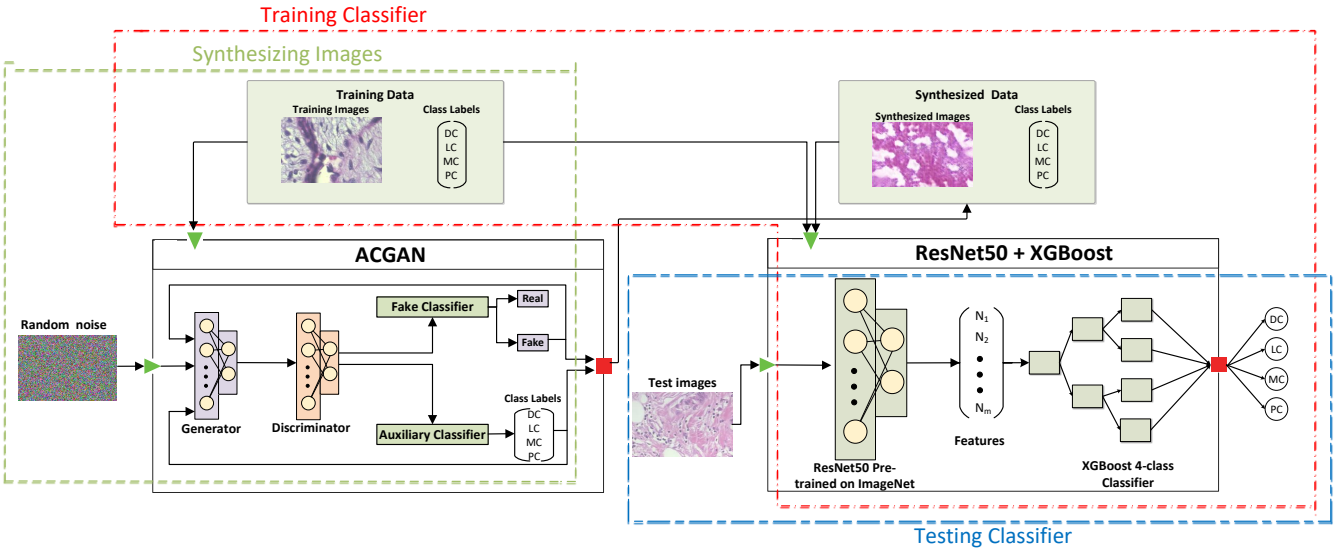


Fig. 1. Overview of the proposed breast histopathological image classification with adversarial image synthesis: We first synthesize breast cancer histopathological images with auxiliary classifier generative adversarial network (ACGAN). In the training step, a pre-trained ResNet50 is used to extract deep convolutional features from both the ACGAN-synthesized images and the existing training images. An extreme gradient boosting tree (XGBoost) is then applied to classify four different cancer sub-types based on the extracted features. For testing, we follow the same methodology to extract features from test images using a ResNet50 and subsequently classify them with XGBoost.

classification problems, thereby significantly improving the overall classification performance.

II. Method

This section describes our proposed breast cancer histopathological image classification method with adversarial learning. Fig. 1 shows an overview of our proposed method. ACGAN is first used to synthesize breast cancer histopathological images in order to increase the size of our training dataset. Convolutional features of the newly synthesized dataset is then extracted using a pre-trained ResNet50. Finally, an XGBoost classifier is used to classify disease labels.

A. Data Augmentation with ACGAN

Generative Adversarial Networks (GANs) are first introduced by Goodfellow et al. in 2014 [14]. The original GAN architecture consists of 2 competing convolutional neural networks called the generator and the discriminator. The generator produces synthetic images from random noise, and the discriminator attempts to distinguish between real and fake images produced by the generator. ACGAN is a variant of GAN which takes the conditional distribution of the dataset into account during image synthesis. In ACGAN, the generator's inputs consist of both a random noise vector and a vector of class labels. The discriminator then takes in the conditionally synthesized images produced by the generator, and discriminates between real and fake images as well as producing predictions of the images' class labels.

ACGAN's loss function consists of 2 parts: the log-likelihood of correctly classifying source (L_s) and the log-likelihood of correctly predicting class labels (L_c). ACGAN's discriminator attempts to maximize $L_c + L_s$ while the generator tries to maximize $L_c - L_s$. Equation (1) and (2) details how L_s and L_c are calculated.

$$\mathrm{L}_s = E[\log P(S = real|X_{real})] + E[\log P(S = fake|X_{fake})], \quad (1)$$

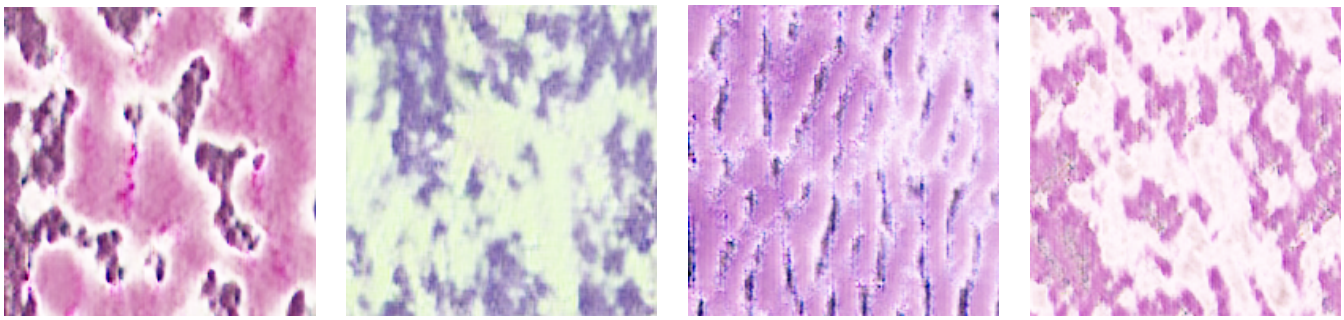
$$\mathrm{L}_c = E[\log P(C = c|X_{real})] + E[\log P(C = c|X_{fake})], \quad (2)$$

where X_{fake} and X_{real} denote generated and real images respectively. $P(S|X)$ shows the probability distribution over all possible images sources, and $P(C|X)$ shows the probability distribution over the class labels of the images.

ACGAN's discriminator does not only provide the probability distributions over sources but also produces probability distributions over the class labels. Motivated by the idea in [15], we use disease labels as conditions (e.g., $C \in \{benign, malignant\}$ or $C \in \{ductal\ carcinoma, lobular\ carcinoma, mucinous\ carcinoma, papillary\ carcinoma\}$), and the adversarial network then learns underlying disease distribution. This method increases the training dataset size with realistic synthetic images along with their corresponding disease labels.

B. Classification with Transfer Learning

We use a transfer learning approach to classify the ACGAN-enhanced breast cancer histopathological image dataset. A transfer learning approach helps the network to train faster and thereby avoiding any potential issues with overfitting. However, unlike other traditional transfer learning approaches where the final layer of pre-trained network is updated for the new dataset, we use the transfer learning approach presented in [13]. In this method, features are first extracted from a ResNet50 which is pre-trained on ImageNet.



(a) DC (b) LC (c) MC (d) PC

Fig. 2. Examples of synthesized images with disease labels generated by ACGAN for 4-class tumor sub-type classification; (a) Ductal Carcinoma (DC), (b) Lobular Carcinoma (LC), (c) Mucinous Carcinoma (MC), (d) Papillary Carcinoma (PC). The generated images not only increases the size of the training dataset but also improves its class balance. These generated images also improves the classification accuracy of dCNN classifiers on the test set. The synthesized images appear to be qualitatively similar and has relevant biological features as the real images.

For the classification step, the extracted convolutional features are fed into an extreme gradient boosting (XGBoost) classifier to determine the cancer type. XGBoost is based on gradient boosted decision which uses gradient descent to minimize error when performing classification [16].

III. Experiment

In this study, we perform breast cancer histopathological image classification with a synthetic image-enhanced training dataset created from the adoption of an ACGAN. We validate the robustness of our transfer learning approach, where the convolutional features are extracted from a pre-trained ResNet50 and classified with an XGBoost classifier.

A. Dataset

In this experiment, we use the Breast Cancer Histopathological Database (BreakHis) [12] [17]. This dataset consist of 7909 images (2480 benign and 5429 malignant images) from 82 patients. Each malignant tumor image is further sub-categorized into four different groups; 3451 ductal carcinoma (DC) images, 626 lobular carcinoma (LC) images, 792 mucinous carcinoma (MC) images and 560 papillary carcinoma (PC) images. Most of the previous research involving this dataset performs binary classification only (benign vs. malignant); However, our experiments include both binary and multi-class tumor-subtype classification (DC vs. LC vs. MC vs. PC) to show the ability of our ACGAN-enhanced dataset to improve the generalizability of dCNN classification networks. We use a random, 70-30 train-test split to generate subsets for training and testing.

B. Implementation Details

Our implementation of ACGAN contains a generator which consists of 5 deconvolution layers with ReLU activation (kernel size 5×5, stride of 2). The ACGAN's discriminator consists of 7 convolutional layers with Leaky ReLU activation (kernel size: 3×3, stride: 2 and dropout: 35%). The discriminator has 2 output layers: the first layer is a sigmoid activation layer which predicts whether the image is real or fake, and the second output layer is a softmax activation which predicts the disease label. The ACGAN is trained for 100 epochs with a batch size of 10 and an initial learning rate of 0.0002 with step decay. For classification, we extract the latent features from the last layer of a pre-trained ResNet50 and apply them to an XGBoost classifier with 100 estimators.

C. ACGAN's Synthesized Images

To create a class-balanced training dataset, we disproportionately synthesize images for underrepresented diseases with our ACGAN. For binary classification, we generate 500 new benign images (20.2% of BreakHis benign images) and 500 new malignant images (9.2% of BreakHis malignant images). For the 4-class classification, we synthesize 300 DC (8.7% of BreakHis DC images), 120 LC (19.2% of BreakHis LC images), 160 MC (20.2% of BreakHis MC images), and 120 PC (21.4% of BreakHis PC images) images respectively.

In Figure. 2, we show several representative examples of synthesized images and their corresponding cancer subtype labels generated by ACGAN. The generated images are realistic and have identical biological characteristics (e.g., enlarged cell, high cellular density, infiltration, nuclear pleomorphism) as the real images without duplicating the original dataset. Therefore, these synthesized images along with their disease labels are added to the existing training dataset without additional pathologists annotations, thereby simultaneously tackling the dataset size and class imbalance challenges in deep learning.

D. Classification Performance

For quantitative evaluation, we measure the classification accuracy of binary and 4-class tumor sub-type classification. To highlight the efficacy of our adversarial image synthesis, we compare the classification performance of our ACGAN-enriched dataset with a dataset enriched with standard data augmentation techniques such as affine transformation. For affine transformation we use horizontal flip, rotation (with degrees equal to 90) and vertical flip. It is worth noting that both data augmentation methods are only applied to

TABLE I

BINARY AND TUMOR SUB-TYPE CLASSIFICATION WITH TWO DIFFERENT DATA AUGMENTATION METHODS (AFFINE BOOSTING VS. ACGAN SYNTHESIS) AND TWO DIFFERENT TRANSFER LEARNING APPROACHES (RESNET50 UPDATE VS. XGBOOST WITH CONVOLUTIONAL FEATURE)

Method	Binary classification	Tumor sub-type classification
Affine boosting + ResNet50 update	80.8	77.45
Affine boosting + XGBoost with convolutional feature	84.17	83.18
ACGAN synthesis + XGBoost with convolutional feature	**90.15**	**86.33**

the training dataset. For reference, we also use a traditional transfer learning approach where the last layer of a pre-trained ResNet50 is fine-tuned with our breast cancer histopathological image dataset. We update the weights of the last layer with an ADAM optimizer and a batch size of 32 for 100 epochs. The initial learning rate is 0.0005.

Table. I summarizes the classification performance. Using ACGAN as data augmentation and extracting convolutional features with ResNet50 followed by XGBoost classifier significantly outperforms the traditional transfer learning approach with affine transformation in both binary and multiclass tumor sub-type classification. With the same dataset enriched by affine transformation, our transfer learning approach with the XGBoost classifier improves the classification accuracy by 3.37% for binary classification and 5.73% for multiclass tumor sub-type classification. This confirms the findings in [13] that XGBoost classifier with convolutional features extracted by ResNet50 is be more robust in dealing with limited datasets.

By using our adversarial image synthesis methodology, the classification accuracy is further increased by 5.98% for binary and 3.15% for multiclass tumor sub-type classification. This indicates that ACGAN aids the training of more robust deep learning classifiers on limited and unbalanced datasets by generating realistic images without repeating them. The results also show that our ACGAN data augmentation method has a large improvement on binary classification in comparison with the multiclass tumor subtype classification due to the distribution of the data.

IV. CONCLUSIONS

Annotated image acquisition is one of the major challenges in the machine learning when applied to the field of medical imaging. In this research, we propose and evaluate ACGAN as a data augmentation method to generate realistic histopathological images and their corresponding disease labels in order to increase the diversity and size of a small dataset. To evaluate the efficacy of our adversarial image synthesis, we perform breast cancer histopathological image classification with a classifier trained on both the original and our ACGAN-augmented datasets. For our classifier, we used a transfer learning approach in which convolutional features are extracted from a pre-trained ResNet50 and classified using XGBoost. Our proposed method significantly improves image classification performance compared with standard transfer learning approaches, consequently introducing a new technique to train classifiers when given small datasets that are highly unbalanced.

REFERENCES

[1] A. G. Waks and E. P. Winer, "Breast cancer treatment: a review," *Jama*, vol. 321, no. 3, pp. 288–300, 2019.

[2] M. T. Islam, B. N. K. Siddique, S. Rahman, and T. Jabid, "Image recognition with deep learning," in *2018 International Conference on Intelligent Informatics and Biomedical Sciences (ICIIBMS)*, vol. 3, 2018, pp. 106–110.

[3] R. J. Mozhdehi and H. Medeiros, "Deep convolutional particle filter for visual tracking," in *2017 IEEE International conference on image processing (ICIP)*, 2017, pp. 3650–3654.

[4] S. Ghosh, N. Das, I. Das, and U. Maulik, "Understanding deep learning techniques for image segmentation," *ACM Computing Surveys (CSUR)*, vol. 52, no. 4, pp. 1–35, 2019.

[5] S. H. Gheshlaghi, O. Dehzangi, A. Dabouei, A. Amireskandari, A. Rezai, and N. M. Nasrabadi, "Efficient oct image segmentation using neural architecture search," in *2020 IEEE International Conference on Image Processing (ICIP)*, 2020, pp. 428–432.

[6] M. H. Motlagh, M. Jannesari, H. Aboulkheyr, P. Khosravi, O. Elemento, M. Totonchi, and I. Hajirasouliha, "Breast cancer histopathological image classification: A deep learning approach," *BioRxiv*, p. 242818, 2018.

[7] F. A. Spanhol, L. S. Oliveira, P. R. Cavalin, C. Petitjean, and L. Heutte, "Deep features for breast cancer histopathological image classification," in *2017 IEEE International Conference on Systems, Man, and Cybernetics (SMC)*, 2017, pp. 1868–1873.

[8] F. A. Spanhol, L. S. Oliveira, C. Petitjean, and L. Heutte, "Breast cancer histopathological image classification using convolutional neural networks," in *2016 international joint conference on neural networks (IJCNN)*, 2016, pp. 2560–2567.

[9] B. Wei, Z. Han, X. He, and Y. Yin, "Deep learning model based breast cancer histopathological image classification," in *2017 IEEE 2nd international conference on cloud computing and big data analysis (ICCCBDA)*, 2017, pp. 348–353.

[10] M. Gour, S. Jain, and T. Sunil Kumar, "Residual learning based cnn for breast cancer histopathological image classification," *International Journal of Imaging Systems and Technology*, 2020.

[11] J. Wang, L. Perez *et al.*, "The effectiveness of data augmentation in image classification using deep learning," *Convolutional Neural Networks Vis. Recognit*, vol. 11, 2017.

[12] Y. Benhammou, B. Achchab, F. Herrera, and S. Tabik, "Breakhis based breast cancer automatic diagnosis using deep learning: Taxonomy, survey and insights," *Neurocomputing*, vol. 375, pp. 9–24, 2020.

[13] N. Lang, D. Saxena, T. Yen, J. Jorns, B. Yu, , and D. H. Ye, "Breast cancer magnification-independent multi-class histopathology classification using dual-step model," in *Proceedings of the 2021 SPIE International Conference on Medical Imaging (SPIE MI 2021)*, February 14–18, 2021.

[14] I. Goodfellow, J. Pouget-Abadie, M. Mirza, B. Xu, D. Warde-Farley, S. Ozair, A. Courville, and Y. Bengio, "Generative adversarial nets," in *Advances in neural information processing systems*, 2014, pp. 2672–2680.

[15] C. N. E. Kan, N. Maheenaboobacker, and D. H. Ye, "Age-conditioned synthesis of pediatric computed tomography with auxiliary classifier generative adversarial networks," in *2020 IEEE 17th International Symposium on Biomedical Imaging (ISBI)*, 2020, pp. 109–112.

[16] T. Chen and C. Guestrin, "Xgboost: A scalable tree boosting system," in *Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining*, 2016, pp. 785–794.

[17] F. A. Spanhol, L. S. Oliveira, C. Petitjean, and L. Heutte, "A dataset for breast cancer histopathological image classification," *IEEE Transactions on Biomedical Engineering*, vol. 63, no. 7, pp. 1455–1462, 2015.