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Deep Learning Data Augmentation for Raman Spectroscopy Cancer Tissue Classification

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ABSTRACT

Recently, Raman Spectroscopy (RS) has demonstrated to be a non-destructive way of cancer diagnosis, due to the uniqueness of RS measurements in revealing molecular biochemical changes between cancerous vs. normal tissues and cells. In order to design computational approaches for cancer detection, the quality and quantity of RS tissues are the basis for accurate prediction. In reality, however, obtaining skin cancer samples is difficult and expensive due to privacy and other constraints. With a small number of samples, the training of the classifier is difficult, and often results in overfitting. Therefore, it is important to have more samples to better train classifiers for accurate cancer tissue classification. To overcome these limitations, this paper presents a novel generative adversarial network based skin cancer tissue classification framework. Specifically, we design a data augmentation module that employs a generative adversarial network to generate synthetic RS samples in different classes. The original tissue samples and the generated data are merged to train classification modules. Experiments on real-world RS data demonstrate that generative adversarial network can be successfully used for data augmentation, in order to train accurate skin cancer tissue classifiers.

Introduction

Skin cancer, one of the most common cancers across the world, accounts for more than 40% of global total cancer cases, in which the top three main types of skin cancers are basal cell skin cancer (BCC), squamous cell skin cancer (SCC), and non-melanoma skin cancer (NMSC)^{1,2}. According to the American Academy of Dermatology Association (AAD), the daily number of diagnosed skin cancer cases in the U.S. is approximately 9,500 and one in five Americans is estimated to develop skin cancer in their lifetime³. Although surgical removal is the optimal method for skin cancer diagnose and treatment, current in situ methods can hardly differentiate cancer from normal skin². In addition, the surgical process is time-consuming and patients may suffer from heavy financial burden⁴. In contrast, the vibrational modes of molecules can be easily and correctly analyzed with Raman Spectroscopy (RS) technique, which is able to detect the differences in the molecular structures of proteins, lipids and pigments of both tumor and normal tissues^{5,6}.

Raman Spectroscopy (RS) is a non-destructive in situ spectroscopic chemical analysis technique that provides detailed information about chemical structure, phase and polymorphism, crystallinity and molecular interaction. RS is an inelastic light scattering technique producing scattered photons either lower in energy (Stokes) or higher in energy (anti-Stokes) than the exciting photons. The energy shifts of the photons correspond to the energies of vibrations of molecules in the sample, thus providing detailed chemical structure information revealing chemical compositions of cells and tissues⁷.

Using RS and machine learning for skin cancer detection has been studied previously⁸, where spectral classification is used to classify BCC based on tissue samples from 55 patient, among which logistic regression classifier using five canonical spectral features obtained from rank-reduced multiclass linear discriminant analysis outperforms the rest classifiers. Previously, we also employed Principal Component Analysis (PCA) to differentiate non-melanoma skin cancer (NMSC) from normal skin with the combination of RS and high-powered CO₂ laser to ablate the tissue surface (an example of laser treatment is shown in Figure 1). In our study⁹, the Raman spectra are collected from both CO₂ treated and untreated samples, and are further used to train a binary logistic regression model to distinguish normal from diseased tissue. This study proves the effectiveness of Raman Spectroscopy-high powered CO₂ method in clinical skin cancer treatment.

Despite of the promising properties, RS suffers from weak signals due to inherent noise. Shot noise and fluorescence's baseline are the most commonly found noise in RS signals. The shot noise is the results of the unavoidable statistical nature of light while the fluorescence's baseline can mask Raman bands with a higher amplitude. Although several denoising method

Figure 1. Examples of normal (a) vs. squamous cell carcinoma tissue (b) specimens. Square regions indicated by the arrows were treated with a high-powered IR laser to ablate the tissue surface. Raman spectra were collected from both ablated and non-ablated regions of the samples. The numbers, 1, 2, and 3, indicate each distinct ablation treatment area.

Figure 2. Raman spectra measured from a dataset with three categories: BCC (basal cell carcinoma), NORMAL, and SCC (squamous cell carcinoma), which are representative of the range of spectra measured in this work. Each sample has 1608 dimensions, where each dimension correspond to the wavelength number of the Raman shift (ranging from 600.237 to 1699.39 cm^{-1}). The value of each dimension represents the Raman intensity. For simplicity, four randomly selected samples in each category are used for visualization. “Treated” means that the sample has been treated using a high-powered IR laser to ablate the tissue surface, or no laser treatment otherwise (“Untreated”).

have been proposed, noise can hardly be effectively removed from the signal to limit the negative impact of the noise, which will damage the integrity of the Raman spectrum^{10,11}. Discrete wavelet transform (DWT) has been applied to separate shot noise, fluorescence’s baseline and informative Raman peaks by decomposing the spectrum into a set of wavelet coefficient and scale coefficient^{12,13}. Other advanced methods adapted based on DWT such as adaptive lifting wavelet transform (ALWT) are also proved effective in removing noise from Raman spectrum¹⁴. In our previous study⁹, the samples were processed with laser ablation, as shown in Figure 1. The study systematically varied the ablation level and examined its impact. The results showed that Raman spectral features from normal and cancerous tissue did not significantly correlate with ablation treatment level (as a result, in this study, we combine both laser treated and untreated samples to maximize the number of available samples).

Another challenge in RS based skin cancer detection is that the data is often ill-posed, because Raman spectrum has a background resulted from skin fluorescence, both the spectra and correlation can be introduced with variance. Apart from that, the number of frequency components in Raman spectrum is normally $10^3 \sim 10^4$, indicating a large dimension of features. In addition, for cancer diagnose, few valuable samples are available due to privacy and other constraints^{15,16}. The data scarcity, combined with high data dimensionality, present difficulties for deep learning algorithms.

The above challenges motivate our research to use Generative Adversarial Network (GAN) based data augmentation method to increase the sample size for RS based skin cancer detection. GAN is a method to generate data resemble to the training data, using two deep networks, the generator, and the discriminator. Candidates are generated by generative network while the discriminative network evaluates. Through the iterative generation and evaluation process, new data, with the same statistics as the original data set, are generated. Using data augmentation, new samples for each category of the original data are generated in order to improve the performance of the downstream classifiers. For data classification part, a deep convolutional neural network (CNN) is designed as the core module to compare with other baseline models. We employ CNN as the classifier for

RS cancer tissue classification, mainly because that CNN has unique convolutional filters to explore correlation of the signal and learn patterns to differentiate signals between different classes.

Related work

Raman Spectroscopy for Skin Cancer Diagnose

Raman spectroscopy has been considered as a promising non-destructive optical technique characterizing the tissue at the molecular level¹⁷. Recent studies reported that Raman spectroscopy (RS) is beneficial to diagnose and study the evolution of human malignancies both in vitro and in vivo¹⁸. It has been widely proved that Raman spectroscopy can be applied to distinguish skin cancers from normal skin tissue and provide more accurate medical diagnosis¹⁹.

Several researches have utilized RS to diagnose skin cancer. Harvey et al.²⁰ evaluated the application of an integrated real-time system of RS for in vivo skin cancer diagnosis. The performance, in terms of ROC (Receiver Operating Characteristic) curve, can be dramatically increased to 0.879 by using a primary module with generic discriminant analysis in lesion classification. Lieber et al.¹⁷ measured Raman spectrum of 21 suspected non-melanoma skin cancers and detected lesions from normal skin yielding 91% specificity and 100% sensitivity. A 95% separation accuracy between normal skin and BCC is achieved by Choi et al.²¹ with Confocal Raman spectra obtained from various skin depths. The research of Fox et al.⁹ shows that RS classification accuracy is not negatively affected by the ablation process and also beneficial to tumor border demarcation. A hybrid fluorescence Raman approach or a non-linear Raman technique can be used to reduce imaging time.

Due to weak Raman intensity caused by the poor scattering efficiency, PCA analysis or Neural Network is required to distinguish skin cancer tissue from normal tissue²¹. Therefore, deep learning methods have been integrated in our study.

Deep Learning for Biosignal Processing

Analysis and interpretation of biological signals are highly intricate research tasks. Deep learning extracts signal's features automatically from raw data with a better performance when amounts of data are available for learning, while traditional machine learning methods to understand and translate biological signals are based on hand-engineered features. Biosignals and deep learning are often utilized to solve specific application, such as health status monitoring, emotion detection, analysis and classification of human gestures, diagnosis for illness and so on. Among all applications, we focus on the support for diagnosis using deep learning.

An image of a skin lesion was successfully transformed into the probability distribution of clinical dermatoses by Andre et al.²² with CNN. It achieved similar performance with all tested experts' judgment on the identification of common cancers and the identification of the deadliest skin cancer. Budak et al.²³ proposed an end-to-end system based on fully convolutional network (FCN) and bidirectional long short term memory (BiLSTM) for detections of breast cancer. A five-fold cross-validation technique was considered to calculate accuracy metric, which showed that their proposed method was better than those preliminary reported results. Mahbod et al.²⁴ used three pretrained deep models, namely AlexNet, VGG16 and ResNet-18, as deep feature generators. The extracted features were sent to support vector machine classifiers, yielding an area under ROC curve of 83.83% for melanoma classification and of 97.55% for seborrheic keratosis classification. Transfer learning method is usually applied in the deep learning structures as well.

All the detecting systems by using deep learning mentioned above are based on large amounts of data. In terms of augmenting image sets, GAN is widely applied to overcome the sensitivity of synthetic data samples for the cancer data classification²⁵. A skin lesion style-based generative adversarial networks (GANs) model is proposed in²⁶ and proved to be effective for generating skin lesion images with high resolution and abundant diversity. Compared to the prior CNN model, classification indexes like accuracy, sensitivity, specificity, average precision and balanced multi-class accuracy have been improved by 1.6%, 24.4%, 3.6%, 23.2% and 5.6% respectively. A method for synthesizing insect pest training images through GAN is put forward to enhance CNN's performances in the reference²⁷. The F1 density of the classifier model trained with GAN-based augmentation is 0.95, outperforming the models trained with traditionally augmented images with an F1-score of 0.92. There is sufficient evidence to prove that by using GAN-based enhancement methods, deep learning classification models have better performances than using traditional enhancement methods.

Problem Definition and Overall Framework

Problem Statement

In this paper, skin cancer tissue classification task can be defined as a multi-class classification problem. In this work, we use the tissue dataset from a previous study⁹, which consists of three tissue categories: BCC (basal cell carcinoma), SCC (squamous cell carcinoma) and NORMAL. Using RS process, each sample is represented by 1,608 dimensions, denoting the frequency of the Raman shift (ranging from 600.237 to 1699.39 wavenumber cm^{-1}), and the value of each dimension represents the Raman intensity. Examples of RS spectra (intensity vs. cm^{-1}) are reported in Figure 2.

Let $X = \{\mathbf{x}^1, \dots, \mathbf{x}^n\}$ denotes the given RS dataset, where n is the number of samples in the dataset, $\mathbf{x}^i \in \mathbb{R}^{1 \times d}$, d is the dimension of each sample. Because we use RS intensity at each wavelength number (cm^{-1}) position as feature values to present each sample, the total feature dimension is $d = 1,608$.

Each sample $\mathbf{x}^i$ is associated with a ground-truth label $\mathcal{Y} \in \{\text{BCC}, \text{Normal}, \text{SCC}\}$. The goal of skin cancer tissue classification is to learn a projection function: $\mathcal{F}(\mathbf{x}^i) \rightarrow \mathcal{Y}$

Overall Framework

Our framework introduces a novel generative adversarial network based medical data augmentation for Raman Spectroscopy cancer tissue classification, as shown in Fig. 3, mainly consists of following two components:

- **Data Augmentation Module.** In order to increase the number of training samples, we employ a Generative Adversarial Network to generate synthetic samples for each class, BCC, SCC, and Normal, respectively. This process will generate different types of samples for data augmentation.
- **Data Classification Module.** Combining original samples and GAN generated sample, the data classifier will learn discriminative models to determine the category of each sample. In our study, we exploit using a deep convolutional neural network (CNN) to classify each sample into respective category, and also comparatively study other rival methods, such as logistic regression (LR), support vector machines (SVM).

Figure 3. Illustration of the generative adversarial network based data augmentation for Raman Spectroscopy cancer tissue classification framework.

Methodology

Figure 3 shows the proposed framework for RS based cancer tissue classification, and the detailed algorithmic procedures are reported in Algorithms 1 & 2. Overall, the framework includes two main modules: Data augmentation module and data classification module. The former will learn to generate synthetic samples for each class, and the latter will learn to classify test samples into correct categories.

Data Augmentation Module

In order to solve the small sample size problem, we propose to use Generative Adversarial Network (GAN) to investigate data augmentation. Generative Adversarial Network (GAN) has been implemented to synthesize high quality data for adding training data in several studies²⁸. As shown in the lower left dashed rectangular box in Figure 3, the GAN includes two major building blocks: generator and discriminator. The two blocks are both consists of multilayer perceptrons.

- The generator G is to generate fake samples from the latent vector z . The generator can be thought of as analogous to a team counterfeiters, trying to produce fake samples and try to induce the discriminator to give the generated sample a higher score.
- The discriminator D is analogous to the police, which tries to discriminate between the original data and the generated samples.

The generator and discriminator are running in an adversarial way to improve each other. Specifically, the discriminator D tries to learn the original data and guides the generator by sending feedback about the generated synthetic samples. The generator G learns from the feedback and tries to generate new samples which are very close to the original data. The discriminator D is trained to maximize the probability of distinguishing original samples from samples generated from the generator G (*i.e.* correctly predict whether a sample is generated or not) The loss function of the discriminator D can be expressed as:

$$\max_D V(G, D) = E_{x \sim p_d} [\log D(x)] + E_{x \sim p_z} [\log(1 - D(G(z)))] \quad (1)$$

Simultaneously, the generator G is trained to minimize $\log(1 - D(G(z)))$, which tries to make generate samples resemble to the genuine training samples, as much as possible. The loss function of the generator G can be expressed as:

$$\min_G V(G, D) = E_{x \sim p_z} [\log(1 - D(G(z)))] \quad (2)$$

In other words, D and G are trained by a two-player minimax game with the loss function:

$$\min_G \max_D V(G, D) = E_{x \sim p_d} [\log D(x)] + E_{x \sim p_z} [\log(1 - D(G(z)))] \quad (3)$$

Data Classification Module

From the data augmentation module, we can obtain a set of new samples for each category of the original data, which will be used to enhance the performance of the classifier. In our classification module, we employ a deep convolutional neural network (CNN) as the core module.

Let $x^i \in \mathbb{R}^d$ be the d -dimensional feature corresponding to the i -th sample. For each sample x^i , we apply a 1-D convolution with a width- k kernel to produce a new feature.

$$f_l^i = \text{ReLU}(w * x_{l:l+k-1}^i + b) \quad (4)$$

where $l \in \{1, 2, \dots, d\}$, w is a filter, and b is a bias term. This filter is applied to each possible window of features in the i -th sample to produce a feature map $\mathbf{f}^i \in \mathbb{R}^{d-k+1}$, where $\mathbf{f}^i = [f_1^i, f_2^i, \dots, f_{d-k+1}^i]$.

In order to obtain multiple features, our classification model uses r filters. So we can obtain a feature matrix $\mathbf{F}^i \in \mathbb{R}^{r \times (d-k+1)}$ for the i -th sample, with $\mathbf{F}^i = [\mathbf{f}_1^i, \mathbf{f}_2^i, \dots, \mathbf{f}_r^i]$. Then, we apply 1D Max pooling to the feature map matrix $\mathbf{F}^i$ to obtain the feature corresponding to all filters:

$$\tilde{\mathbf{F}}^i = \text{Maxpooling}(\mathbf{F}^i) \quad (5)$$

where $\tilde{\mathbf{F}}^i \in \mathbb{R}^{(d-k+1)}$. The feature $\tilde{\mathbf{F}}^i$ is passed to a fully connected layer with softmax function to predict the label of i -th sample.

$$\hat{y}^i = \sigma(W_3 * \tilde{\mathbf{F}}^i + b) \quad (6)$$

where $\sigma(\cdot)$ is the softmax activation function, $\hat{y}^i$ denotes the predicted probabilities of the i -th data.

Classification Loss

The classification loss $\mathcal{L}(\Theta)$ is to minimize the cross-entropy for the labeled data:

$$\mathcal{L}(\Theta) = -\frac{1}{N} \sum_{i=1}^N y_i \log(\hat{y}_i), \quad (7)$$

where N is the sum of the number of original samples and generated samples. y_i denotes the label of the i -th data, $\hat{y}_i$ are the classification prediction for the i -th data, respectively.

Algorithm 1: DL-DA: Deep Learning Data Aggregation for Cancer Tissue Classification

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Input: (1) $\mathcal{D}$: Labeled RS tissue sample dataset
(2) $\{p_g(z), \kappa\}$: Noise prior for GAN and # of steps training GAN discriminator
(3) ρ : Data augmentation ratio

Output: $()$: Suitably trained DeepRS classifier

```
1  $\tilde{\mathcal{D}} \leftarrow \emptyset$ 
2 for each class  $c$  of training samples in  $\mathcal{D}$  do
3    $\mathcal{D}^c \leftarrow$  Samples labeled as class  $c$  in  $\mathcal{D}$ 
4    $\tilde{\mathcal{D}}^c \leftarrow \text{DA}(\mathcal{D}^c, p_g(z), \kappa, \rho)$  # Algorithm 2
5    $\tilde{\mathcal{D}} \leftarrow \tilde{\mathcal{D}} \cup \tilde{\mathcal{D}}^c \cup \mathcal{D}^c$ 
6 end
7  $\mathbf{F}(\tilde{\mathcal{D}}) \leftarrow$  Apply 1-D Convolutional to  $\tilde{\mathcal{D}}$ 
8  $\tilde{\mathbf{F}}(\tilde{\mathcal{D}}) \leftarrow$  Apply max pooling to feature map  $\mathbf{F}(\tilde{\mathcal{D}})$ 
9  $() \leftarrow$  Apply two dense layers neural networks to  $\tilde{\mathbf{F}}(\tilde{\mathcal{D}})$ 
10 return  $()$ 
```

Algorithm 2: DA: Data Augmentation Algorithm

Input:

(1) $p_g(z)$: Noise prior for GAN training
(2) $X = \{x^1, \dots, x^n\}$: Original data of each class
(3) κ : # of steps for GAN discriminator training

Output: Augmented data

```
1 for number of training iterations do
2   for  $\kappa$  step do
3     Sampling  $n$  noise samples  $\{z^1, \dots, z^n\}$  from noise prior  $p_g(z)$ ;
4     Update the discriminator by maximizing the Eq. (1);
5   end
6   Sampling  $n$  noise samples  $\{z^1, \dots, z^n\}$  from noise prior  $p_g(z)$ ;
7   Update the generator by minimizing the Eq. (2);
8 end
```

Data Augmentation Algorithm Description

Algorithm 1 lists the detailed procedures of the proposed algorithm for RS based cancer tissue classification. Algorithm 2 lists the RSDA data augmentation module, which is used in Algorithm 1.

Given a noise prior $p_g(z)$ and original data of each class $X = \{x^1, \dots, x^n\}$, the goal of RSDA data augmentation module is to generate new samples for each class of original data. The process is alternated between k steps of optimizing discriminator D and one step of optimizing generator G . Firstly, we maximize the loss function of discriminator (Step 3-4). After k steps, we then minimize the loss function of generator (Step 6-7). After the training process, we add the generated new samples to the original dataset to expand the training dataset to learn convolutional neural networks for classification.

Experiments

Experimental Setup

Benchmark Datasets: Benchmark data used for the experiments were originally collected from Strasswimmer Mohs Surgery, Delray Beach, FL, where the data are used for a study to validate impact of laser treatment for SCC vs. normal tissue classification⁹. Further information about the tissue preparation, treatment, and laser used for the Raman measurements are

Table 1. Statistics of the benchmark RS data.

Category	# of Treated	# of UNTreated	# of All data
BCC	2	34	36
NORMAL	28	35	63
SCC	20	30	50

Table 2. Performance comparison between proposed method (DL-DA_b) vs. baselines, using balanced data augmentation.

Methods	All Data			Treated			UNTreated		
	Acc	F1	AUC	Acc	F1	AUC	Acc	F1	AUC
LR	0.685	0.628	0.848	0.800	0.550	0.833	0.626	0.601	0.830
PCA_LR	0.362	0.350	0.562	0.420	0.357	0.548	0.333	0.330	0.548
LR-DA _b	0.685	0.619	0.877	0.820	0.563	0.897	0.616	0.587	0.861
SVM	0.745	0.716	0.895	0.840	0.582	0.908	0.697	0.692	0.880
PCA_SVM	0.752	0.723	0.890	0.800	0.651	0.908	0.727	0.720	0.874
SVM-DA _b	0.765	0.744	0.921	0.820	0.563	0.909	0.737	0.733	0.910
MLP	0.745	0.721	0.898	0.820	0.562	0.896	0.707	0.703	0.886
MLP-DA _b	0.812	0.798	0.922	0.860	0.590	0.927	0.788	0.789	0.909
LSTM	0.724	0.717	0.892	0.740	0.602	0.824	0.717	0.717	0.905
LSTM-DA _b	0.799	0.777	0.933	0.880	0.763	0.949	0.758	0.754	0.923
CNN	0.772	0.757	0.912	0.860	0.589	0.881	0.727	0.728	0.902
DL-DA_b	0.826	0.807	0.945	0.900	0.610	0.939	0.788	0.786	0.933

also detailed in the publication⁹. In our study, all RS data used in the experiments were reprocessed and de-identified. From the processed data, we create a dataset with three categories: BCC (basal cell carcinoma), NORMAL and SCC (squamous cell carcinoma), each contains 36, 63, and 50 RS samples, respectively. Each sample has 1,608 dimensions, representing the wavelength numbers of the Raman shift (ranging from 600.237 to 1699.39 cm⁻¹). The value of each dimension represents the Raman intensity. The details of the benchmark RS data are reported in Table 1.

Data Augmentation: In order to study how will data augmentation impact on the classifier performance, we propose two augmentation approaches:

- **Balanced Data Augmentation (DA_b):** This approach intends to introduce same amount of synthetic samples to each class. Using data augmentation, we generate n' new samples for each class (each sample has 1,608 dimensions). Thence, the number of BCC, NORMAL and SCC dataset increase to $n' + 36$, $n' + 63$ and $n' + 50$, respectively. After that, all samples are combined to form a training dataset with $3 * n' + 149$ samples.

In order to consider the impact of the different augmentation sample size generated on the classification results, we set four different sample sizes, $n' = 128$, $n' = 256$, $n' = 512$, $n' = 1,024$, respectively.

- **Stratified Data Augmentation (DA_s):** This approach intends to maintain the same class prior probability during the data augmentation process, by generating a different number of augmentation samples for each category according to the proportion m between the different categories of the original data. For example, the number of augmentation samples is $m * 36$ for BBC, $m * 63$ for NORMAL, and $m * 50$ for SCC class, respectively.

Evaluation Metrics: The skin cancer tissue classification is a multi-class classification task, whose evaluation measure is commonly the Accuracy metric. However, when datasets suffer from class imbalance, it goes less reliable. Therefore, in addition to the Accuracy metric, we add Macro-F1 and Area Under Curve (AUC). For all experiments, we use leave-one-out cross validation on total samples throughout the experiments.

Baselines

We implement following baselines for comparisons to demonstrate the effectiveness of our proposed model.

- **LR** is a Logistic Regression model, which directly feed the sample features into the Softmax classifier to determine the category.
- **PCA_LR** first uses Principal Component Analysis (PCA) to reduce the input features to 100 dimensions, and then trains logistic regression classifier for classification.
- **LR-DA_x** applies linear regression (LR) to the augmentation of original and synthetic data, and train an LR model for classification. We will study both balanced ($x = b$) and stratified augmentation ($x = s$) in the experiments.
- **SVM** is a support vector machine classifier learned in the original feature space.
- **PCA_SVM** uses PCA to reduce input features to 100 dimensions, then trains SVM classifiers for classification.

Table 3. Performance comparison between the proposed method method (DL_DA_s) against the baselines, using stratified data augmentation (m : the augmentation data for each category is m as many as the original sample).

Methods	All Data			Treated			UNTreated		
	A	F1	AUC	A	F1	AUC	A	F1	AUC
LR	0.685	0.628	0.848	0.800	0.550	0.833	0.626	0.601	0.830
LR_DA _s ($m = 1$)	0.671	0.563	0.850	0.840	0.569	0.866	0.586	0.521	0.832
LR_DA _s ($m = 2$)	0.678	0.589	0.861	0.820	0.556	0.897	0.606	0.557	0.841
SVM	0.745	0.716	0.895	0.840	0.582	0.908	0.697	0.692	0.880
SVM_DA _s ($m = 1$)	0.691	0.627	0.901	0.820	0.554	0.900	0.626	0.596	0.891
SVM_DA _s ($m = 2$)	0.725	0.670	0.903	0.820	0.556	0.900	0.677	0.651	0.901
MLP	0.745	0.721	0.898	0.820	0.562	0.896	0.707	0.703	0.886
MLP_DA _s ($m = 1$)	0.758	0.736	0.904	0.820	0.562	0.893	0.727	0.724	0.891
MLP_DA _s ($m = 2$)	0.758	0.739	0.910	0.820	0.562	0.905	0.727	0.726	0.896
LSTM	0.724	0.717	0.892	0.740	0.602	0.824	0.717	0.717	0.905
LSTM_DA _s ($m = 1$)	0.845	0.836	0.934	0.860	0.708	0.880	0.838	0.838	0.937
LSTM_DA _s ($m = 2$)	0.818	0.805	0.952	0.880	0.763	0.963	0.788	0.786	0.940
CNN	0.772	0.757	0.912	0.860	0.589	0.881	0.727	0.728	0.902
DL_DA _s ($m = 1$)	0.772	0.751	0.922	0.860	0.590	0.861	0.727	0.726	0.910
DL_DA _s ($m = 2$)	0.785	0.763	0.926	0.840	0.577	0.868	0.758	0.754	0.917

Table 4. Impact of the convolution kernel width k , using balanced data augmentation ($n'=512$).

Methods	All Data			Treated			UNTreated		
	Acc	F1	AUC	Acc	F1	AUC	Acc	F1	AUC
CNN ($k=3$)	0.765	0.751	0.904	0.840	0.576	0.865	0.727	0.728	0.898
DL_DA _b ($k=3$)	0.812	0.791	0.939	0.900	0.610	0.930	0.768	0.766	0.928
CNN ($k=4$)	0.765	0.751	0.910	0.840	0.576	0.873	0.727	0.728	0.901
DL_DA _b ($k=4$)	0.826	0.806	0.943	0.900	0.610	0.934	0.788	0.786	0.931
CNN ($k=5$)	0.772	0.757	0.912	0.860	0.589	0.881	0.727	0.728	0.902
DL_DA_b ($k=5$)	0.826	0.807	0.945	0.900	0.610	0.939	0.788	0.786	0.933

- **SVM_DA_x** applies SVM to the augmentation of the original and synthetic data, using both balanced augmentation ($x = b$) and stratified augmentation ($x = s$), and trains an SVM model for classification.
- **MLP** is a Multilayer Perceptron network, which consists of multiple fully connected layers.
- **MLP_DA_x** applies MLP to the augmentation of the original and synthetic data, using both balanced augmentation ($x = b$) and stratified augmentation ($x = s$), and train an MLP model for classification.
- **LSTM** is a long short-term memory neural network capable of learning features from long sequence input.
- **LSTM_DA_x** applies LSTM to learn feature representation from augmentation of the original and synthetic data, using both balanced augmentation ($x = b$) and stratified augmentation ($x = s$). Finally, we deploy a fully connected layer with corresponding activation function to predict the class of samples.
- **CNN** uses a convolution neural network to learn sample representations by sliding windows on sample features.
- **DL_DA_x** is our deep learning model for RS based cancer tissue classification. We use CNN to learn feature representation from the augmentation of the original and synthetic data, using both balanced augmentation ($x = b$) and stratified augmentation ($x = s$), followed by a pooling and a dense layer with softmax function, to predict class label of each sample.

Implementation Details

For training, we use 500 epochs for all model. For data augmentation module training, we use the Adam optimizer with the initial learning rate of 0.0002 to train the GAN model, and then generate a certain number of augmentation samples for each class. In GAN, the generator is composed of one fully-connected layer with 100 hidden units and three fully-connected

Table 5. Impact of the data augmentation sample size n' , using balanced data augmentation and kernel width $k=5$.

Methods	All Data			Treated			UNTreated		
	Acc	F1	AUC	Acc	F1	AUC	Acc	F1	AUC
DL $_{DA_b}$ ($n'=128$)	0.812	0.796	0.929	0.880	0.596	0.868	0.777	0.776	0.920
DL $_{DA_b}$ ($n'=256$)	0.799	0.778	0.935	0.900	0.610	0.908	0.748	0.747	0.923
DL$_{DA_b}$ ($n'=512$)	0.826	0.807	0.945	0.900	0.610	0.939	0.788	0.786	0.933
DL $_{DA_b}$ ($n'=1024$)	0.812	0.793	0.946	0.880	0.610	0.923	0.778	0.776	0.936

Table 6. Impact of the data augmentation sample size n' , using stratified data augmentation and kernel width $k=5$ (m represents that the augmentation data for each category is m as many as the original sample).

Methods	All Data			Treated			UNTreated		
	A	F1	AUC	A	F1	AUC	A	F1	AUC
DL $_{DA_s}$ ($m=1$)	0.772	0.751	0.922	0.860	0.590	0.861	0.727	0.726	0.910
DL $_{DA_s}$ ($m=2$)	0.785	0.763	0.926	0.840	0.577	0.868	0.758	0.754	0.917
DL $_{DA_s}$ ($m=4$)	0.805	0.787	0.936	0.880	0.604	0.886	0.768	0.767	0.927
DL$_{DA_s}$ ($m=6$)	0.832	0.816	0.944	0.900	0.610	0.912	0.798	0.797	0.935
DL $_{DA_s}$ ($m=8$)	0.825	0.813	0.928	0.920	0.625	0.905	0.778	0.778	0.911

(a) Original samples. **(b)** GAN generated samples.**Figure 4.** Visualization of the distributions of the original samples (a) vs. GAN generated samples (b), in the RS spectra feature space using t -SNE²⁹. Each dot denotes a sample, color-coded by the label where red, blue, green denote BCC, SCC, Normal, respectively (using balanced data augmentation with $n'=128$).

layers with 64 hidden units, which are activated using Rectified Linear unit (ReLU). Furthermore, each fully-connected layer is followed by a Batch Normalization. The discriminator is composed of one fully-connected layer with 1,608 hidden units and two fully-connected layers with 64 hidden units, activated using LeakyReLU. For classification module of CNN, the number of convolution filters r and their width/size k are set to 120 and 5, respectively. The classification module of LR has one fully-connected layer with the number of hidden units 3, which is activated using Softmax. For classification module of SVM, the $Maxiter$ of LinearSVC is set to 500. The MLP classification module has three fully-connected layers activated by Rectified Linear unit (Relu), and the hidden units of each fully connected layer are set to 100, 32, and 3 respectively. The LSTM classification model consists of an LSTM layer with 100 hidden units and three fully-connected layers with 10, 500, and 3 hidden units, respectively. For each network, we use a fixed learning rate $1e^{-3}$. All deep learning algorithms are implemented using Tensorflow and are trained with Adam optimizer.

Results and Analysis

Tables 2 and 3 reports the performance comparisons (Accuracy, Macro F1 score, and AUC) between the proposed method again baselines, using balanced data augmentation (Table 2) and stratified data augmentation (Table 3), respectively. From the results, we have following observations:

Figure 5. The confusion matrix of the proposed DL_DA.

- (1) Most deep network models, such as CNN and LSTM, outperform traditional machine learning model, like LR and SVM. This demonstrates that deep learning methods, even with limited training samples, can learn better hidden representations of samples. This is because that deep learning can better leverage correlation in the RS signals to learn patterns, whereas LR and SVM take raw RS spectra as features, where feature correlation will deteriorate the classifier performance.
- (2) Models with data augmentation (*e.g.*, MLP_DA_b, CNN_DA_b, LSTM_DA_b) have better performances than single classifier models (*e.g.*, MLP, CNN, LSTM), which shows that the augmentation module can improve the performance of classifier models.
- (3) In the ability of improving classification accuracy, CNN_DA_b and LSTM_DA_b is better than SVM_DA_b and LR_DA_b, confirming that the addition of augmentation module will be more effective for deep network models. This is probably because the deep network needs more data to satisfy the requirements of the model.
- (4) Compared with all baselines, our proposed DL_DA_b achieves the best performance and outperforms other classification method with augmentation module in most cases. The superiority of DL_DA_b is attributed to its data augmentation which provides new samples to help the classification model consistently perform well when few samples are available for training.
- (5) When the data is augmented according to the proportion of the categories in the original data, as shown in Table 3, we can observe that LSTM_DA_s can achieve the best result. However, our proposed DL_DA_s achieves the competitive performance and outperforms other classification method with augmentation module in most cases.

Parameter Analysis

Impact of the convolution kernel width k : In order to study the impact of the convolution kernel width k , we use balanced data augmentation by adding $n'=512$ samples to each class, and vary k from 3 to 5. The results, reported in Table 4, show that only minor differences are observed using different k values. Overall, using $k=5$, our model DL_DA_b can obtain the best performance.

Impact of the sample size n' :

- **Balanced Data Augmentation:** Using balanced data augmentation, we set the augmentation sample size n' to 128, 256, 512, 1024, respectively, and report the results in Table 5. The results show as the number of augmentation sample size n' increases, the classification accuracy continues to improve, but when the number of n' increases to 1024, the various evaluation indicators will decrease, which may be due to the imbalance between the original data and the augmentation data.
- **Stratified Data Augmentation:** Using stratified data augmentation, we set the m to 1, 2, 4, 6 and 8. For example, when $m=2$, the data augmentation module will generate $2*36$, $2*63$, $2*50$ augmentation samples for the BCC, NORMAL and SCC dataset, respectively, and their training samples will increase to $2*36+36$, $2*63+63$ and $2*50+50$, respectively. We report the results in Table 6. The results show as the number of the m increases, the classification accuracy continues to improve, but when the number of m increases to 8, the various evaluation indicators will slightly decrease.

Case Study

Data distribution visualization

In order to verify the effectiveness of the augmentation module of our model, we visualize the original data and new samples generated by the generative adversarial network.

From Fig. 4(a), we can observe that the distribution of the original data is more scattered and difficult to distinguish, due to the small amount of data. Otherwise, From Fig. 4(b), we can observe that compared with original samples, different class of samples generated by GAN are easy to distinguish (we use balanced data augmentation with $n'=128$). The results show that generated samples not only expand the coverage of training dataset, but also preserve the key feature distributions of the original data.

The Confusion Matrix

In order to verify the effectiveness of DL_DA in differentiating different class samples, Fig. 5 reports the confusion matrix of DL_DA on all data (we use balanced data augmentation, using $n'=128$ and kernel size $k=5$). The results show that DL_DA remains a high accuracy in separating different type of tissue samples.

Conclusions

In this paper, we proposed to use deep learning for Raman Spectroscopy based cancer tissue classification, by using data augmentation method to increase the number of training samples in order to enhance downstream classifiers for better feature representation learning from RS signals and better classification. To achieve the goal, we proposed a novel generative adversarial network based skin cancer tissue classification framework with two major components: (1) Data augmentation module, and (2) Data classification module. The former employs a Generative Adversarial Network for data augmentation to obtain a sufficient number of data, and the latter uses five different approaches for classification. Our study validated different ways of data augmentations, including balanced data augmentation to add same number of samples to each class and stratified data augmentation to preserve class distributions. Experiment results show that GAN can be successfully utilized for augmenting data and generating synthetic samples resemble to the original samples. Moreover, the proposed DL_DA (using GAN to generate augmentation samples and CNN for final classification) obtains the best performance to separate BCC, and SCC cancer, from normal samples.

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Author contributions statement

Drafting of the manuscript: M.W., S.W., S.P., X.Z.; Design and modeling: M.W., S.W., S.P., X.Z.; Data collection: A.T., J.S.; Data analysis & experiments: M.W., S.W.; Obtained funding: X.Z.; Supervision: X.Z.

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