Epileptic Focus Localization Based on iEEG by Using Positive Unlabeled (PU) Learning

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***Abstract*—Epilepsy is a chronic disorder of the brain. Intracranial electroencephalogram (iEEG) recorded from cortex is the most popular measurement for not only the diagnosis of epilepsy, but also the focus localization that is crucial for the surgery. In recent years, the machine learning methods have been rapidly developed and applied successfully to various real world problems. Given sufficient number of samples, the powerful deep learning methods can achieve high performance for epileptic focus localization. However, it is a challenging task to obtain large amount of labeled iEEG regarding focal/non-focal channels, since the annotations must be performed by multiple clinical experts through visual judgment on the long term iEEG signals. In order to reduce the necessary number of labeled training samples, we introduce the positive unlabeled (PU) learning method for classification of focal and non-focal epileptic iEEG signals. The proposed method enables us to learn a binary classifier by using small amount of labeled data containing only one class (i.e., focal signals) and unlabeled data containing two classes (i.e., focal and non-focal signals), which greatly reduces the workload of clinical experts for annotations. Experimental results on Bern dataset and iEEG recorded from Juntendo University Hospital demonstrate the effectiveness of our method.**

I. Introduction

Epilepsy is a chronic brain disease in the world which caused by abnormal discharges in the brain [1]. According to World Health Organization (WHO, http://www.who.int/), approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally. Usually we can control epileptic seizures through medications, but some patients with epilepsy are resistant to medications, hence the common treatment is to remove epilepsy focus by surgery. Before the surgery, we first need to locate the epileptic focus precisely by using the various brain signals or neuroimaging measurements. As compared to other brain signal recording methods, iEEG is widely used for epileptic focus localization because of the advantage of high temporal resolution [2]. The iEEG signals, recorded from epileptogenic area, are called focal signal, while the signals, recorded from non-epileptogenic area, are called non-focal signal. Many studies have shown that there are some spike waves (sharp wave, spike, slow wave, etc.) in the focal signals [3]. At present, the clinical experts diagnose epilepsy through the visual judgment based on the spike waves, which is an extremely time consuming and difficult process. In addition, the qualified clinical experts for such diagnosis are fairly scanty in Japan as well as other countries. Therefore, it is an imperious demand to relieve the heavy workload of clinical experts by applying powerful machine learning methods.

In recent years, many machine learning methods have been proposed for the epileptic focus localization problem. The classification of focal and non-focal iEEG signals is studied in [4], in which the discrete wavelet transform (DWT) is used for feature extraction, leading to the best classification accuracy of 84% by using some typical classifiers k-nearest neighbor (KNN), probabilistic neural network (PNN), fuzzy classifier and least squares support vector machine (LS-SVM). In [5], the entropy is employed to extract features from epileptic iEEG signals, resulting in the classification accuracy of 87% by applying the classifier of LS-SVM. In [6], the authors apply the empirical mode decomposition (EMD) to extract intrinsic mode functions (IMFs), which can be also used as the inputs of LS-SVM classifier. By using this approach, the classification accuracy of 87% can be achieved.

All the methods mentioned above can achieve promising results on epileptic focus localization. However, the significant drawback in these methods is that a large amount of labeled data must be provided by the clinical experts. To obtain such labeled data, each 20 seconds iEEG signals must be judged visually by multiple clinical experts to provide the final label of this segment, which is still a time consuming and extremely difficult process. Therefore, in the real scenarios, acquiring a large amount of reliable and labeled epileptic data remains a challenging task. This indicates that although the supervised learning methods can obtain the excellent performance on epileptic focus localization, but they are not practical for real-world diagnosis.

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To tackle this challenging problem, this study mainly address an issue that how to significantly reduce the necessary amount of labeled data without deteriorating the performance. To achieve this goal, we first formulate the epileptic focus localization problem under the PU learning framework, which can thus be solved by employing the PU algorithms. More specifically, we can use the small amount of labeled data containing only one class (focal signals) and a large amount of unlabeled data containing two classes (focal and non-focal signals) to train an unbiased classifier for classification of focal/non-focal signals. Based on the classification results, the focal locations can be precisely identified by the specific clinical criteria. Therefore, our method is able to significantly relieve the heavy workload of clinical experts, while achieving the comparable performance on epileptic focus localization.

II. Methodology

The detection of focal or non-focal channels is often performed on the segmentation of iEEG signals. Each segment is usually 20 seconds, which can be visually diagnosed by the clinical experts. Therefore, we follow the traditional clinical diagnosis strategy to firstly perform the segmentation of iEEG signals. Considering each 20 seconds segment of iEEG as one sample, we can then collect many data samples for training the machine learning method.

In this work, we employ the feature extraction method proposed by [7], in which the relationship between frequency band and entropy feature is discussed. By using the entropy measurements on different bandpass filtered iEEG signals, we can obtain not only the discriminative features but also the physical interpretation that is much appreciated by clinical experts. Therefore, we firstly use several bandpass filters to process the iEEG segments, then calculate several different entropies on the each filtered segments, which can thus be used as the feature representation of each iEEG segment. Finally, based on partially labeled focal segments, the PU learning is employed for epileptic focus and non-focus classification. The flowchart of our method is shown in the Fig. 1.

A. Dataset and Preprocess

In our paper, we use two datasets, one is the public dataset (Bern-Barcelona Database) and the other dataset is recorded from the patients at Juntendo University Hospital.

1) Bern-Barcelona Dataset: One iEEG dataset used in this paper is obtained from the Bern-Barcelona iEEG database (http://ntsa.upf.edu/downloads/andrzejak-rg-schindler-k-rummel-c-2012-nonrandomness-nonlinear-dependence-and). You can find a detailed description of this dataset in [8]. This dataset is collected from five patients suffering from pharmacoresistant focal onset epilepsy, consists of 3,750 pairs of focal signals and 3,750 pairs of non-focal signals, every signal has 10,240 samples (20 seconds with 512 Hz sampling frequency), and all the signals are bandpass filtered between 0.5 and 150 Hz by use a fourth-orders Butterworth filter.

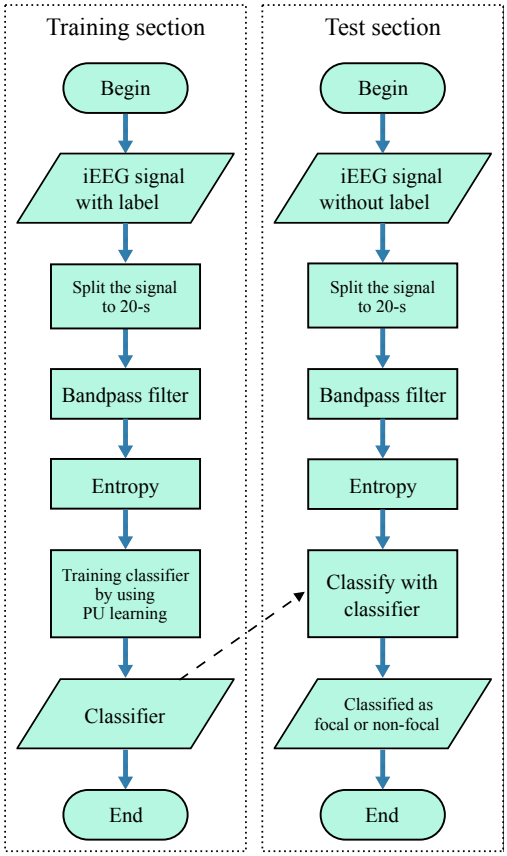

Fig. 1: Flowchart of focal and non-focal signal classification.

2) Juntendo Dataset: The other iEEG dataset used in this paper was recorded at Juntendo University Hospital (Tokyo, Japan). This dataset is recorded from patients who are suffering from temporal lobe epilepsy caused by focal cortical dysplasia. In this paper, we use one patient's data, which includes 60 channels recored during two hours with sampling rate of 2,000 Hz. The label of focal signal was assigned to the channel judged to be a seizure onset electrode by experts, and a non-focal label was given to the rest channels. A example of focal and non-focal signals are visualized in Fig. 2.

B. Feature Extraction

In this paper, we use seven different bandpass filters and eight different entropies for data features extraction. The flowchart of feature extraction is shown in Fig. 3.

1) Split frequency band: iEEG signals are processed by seven different bandpass filters, the frequency selection of bandpass is based on the commonly used physiological values. In this paper, seven different bandpass filters we used are as follows: Delta (0.5-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), Beta (13-30 Hz), Gamma (30-80 Hz), Ripple (80-250 Hz) and Fast Ripple (250-600 Hz).

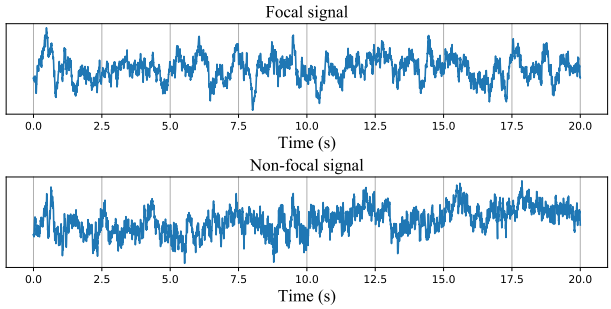

Fig. 2: Focal and non-focal signals

2) Entropy: After iEEG signals are processed by bandpass filter, we calculate eight different entropies for each filtered signal. The entropies we used are shown as follows: Shannon entropy, Renee entropy, Generalized entropy [9] [10], Phase entropy (two kinds) [11], Approximate entropy [12], Sample entropy [13], Permutation entropy [14]. Each entropy can reflect different statistical properties of filtered iEEG signals. By concatenating eight entropies under seven band-pass filtered signals, we can obtain a 7×8 feature representation for each segment of iEEG signals.

C. PU Learning for Classification

The PU learning model is shown in Fig. 4. In this model, only a small amount of data is labeled, which belongs to only one specific class, and the other data are unlabeled. In contrast to the supervised methods, PU learning only needs a small number of labeled samples together with unlabeled samples. Unlike the semi-supervised learning, PU learning does not need the labeled data for both two classes.

More specifically, PU learning is defined as learning from positive and unlabeled data, which can be regarded as a two classes (positive and negative) classification method. At present, according to the strategy how to deal with unlabeled data, PU learning can be divided into two categories. One category is to find the reliable negative data (RN) in unlabeled data [15] [16] [17], based on which we can apply the standard supervised learning methods for binary classifications. Another category is to treat the unlabeled data as negative data, and give a suitable weight for unlabeled data [18] [19] [20].

Let $\mathbf{x}$ be the input feature vector calculated from one segment of iEEG, $y \in \{\pm 1\}$ be the class label, i.e., $+1$ denotes focal signal and -1 denotes non-focal signal. The class conditional distributions for focal signals, denoted by $p_p(\mathbf{x})$, and non-focal signals, denoted by $p_n(\mathbf{x})$, are defined by

$$\begin{aligned} p_p(\mathbf{x}) &= p(\mathbf{x} \mid y = +1), \\ p_n(\mathbf{x}) &= p(\mathbf{x} \mid y = -1). \end{aligned} \tag{1}$$

The prior probabilities for each class are denoted by $\pi_p = p(y = +1)$ and $\pi_n = p(y = -1)$, respectively. Thus, it is obvious that $\pi_n = 1 - \pi_p$. In this PU learning method, π_p is assumed known in advance. By applying the Bayesian rules, the marginal distribution of unlabeled data (i.e. the distribution of both two classes data), denoted by $p(\mathbf{x})$, can be written as

$$p(\mathbf{x}) = \pi_p p_p(\mathbf{x}) + \pi_n p_n(\mathbf{x}). \tag{2}$$

To solve the PU problem, the most popular and successful objective function is the empirical unbiased risk estimator that is proposed by [21] [22] [23], which is

$$\hat{R}_{pn}(g) = \pi_p \hat{R}_p^+(g) + \pi_n \hat{R}_n^-(g), \tag{3}$$

where $\hat{R}_p^+(g)$ and $\hat{R}_n^-(g)$ denotes the empirical risks for focal and non-focal data, respectively. The $g(\cdot)$ denotes the binary classification function and $\ell(g(\mathbf{x}), \pm 1)$ denotes the loss function. Thus, the empirical risk for focal signal, i.e., $\hat{R}_p^+(g)$ in (3), can be calculated by

$$\hat{R}_p^+(g) = \mathbb{E}_{\mathbf{x} \backsim p_p(\mathbf{x})} \ell(g(\mathbf{x}), +1), \tag{4}$$

and the empirical risk for non-focal signal, i.e., $\hat{R}_n^-(g)$, can be calculated by

$$\hat{R}_n^-(g) = \mathbb{E}_{\mathbf{x} \backsim p_n(\mathbf{x})} \ell(g(\mathbf{x}), -1). \tag{5}$$

Since the distribution of non-focal signal is unknown due to that the labels are only given for focal signals, $\hat{R}_n^-(g)$ in (5) cannot be computed straightforwardly. As we can see from (2), the distribution of non-focal signals can be represented by using

$$\pi_n p_n(\mathbf{x}) = p(\mathbf{x}) - \pi_p p_p(\mathbf{x}). \tag{6}$$

Hence, the empirical risk for non-focal samples can be computed by

$$\pi_n \hat{R}_n^-(g) = \hat{R}_u^-(g) - \pi_p \hat{R}_p^-(g), \tag{7}$$

where $\hat{R}_u^-(g)$ and $\hat{R}_p^-(g)$ are the empirical risks under the distribution of unlabeled data and focal data, respectively, which are defined by

$$\begin{aligned} \hat{R}_u^-(g) &= \mathbb{E}_{\mathbf{x} \backsim p(\mathbf{x})} \ell(g(\mathbf{x}), -1), \\ \hat{R}_p^-(g) &= \mathbb{E}_{\mathbf{x} \backsim p_p(\mathbf{x})} \ell(g(\mathbf{x}), -1). \end{aligned} \tag{8}$$

Finally, the risk estimator in (3) can be approximated indirectly by

$$\hat{R}_{pu}(g) = \pi_p \hat{R}_p^+(g) + \hat{R}_u^-(g) - \pi_p \hat{R}_p^-(g). \tag{9}$$

In general, $g(\mathbf{x})$ can be any classifier functions, such as linear discriminative analysis or support vector machines. Due to the recent great success of deep neural networks, in this study, we employ three fully connected layers based neural network as the binary classifier function $g(\mathbf{x})$. Based on the objective function shown in (9), we can thus easily employ the BP algorithm to learn the deep neural network for PU problem.

III. Experimental Results

In this paper, we use two datasets and each dataset is performed by PU learning and fully connected neural network, respectively.

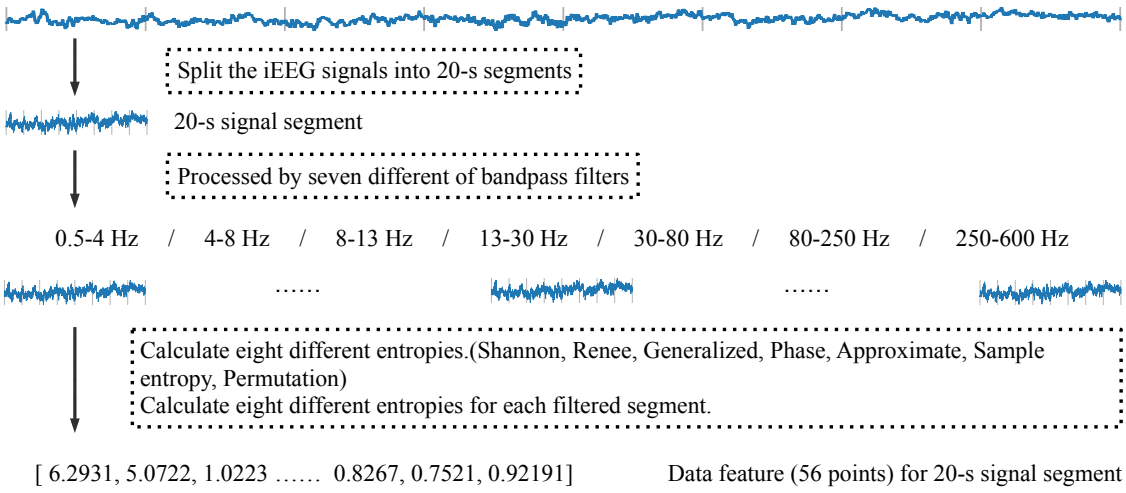

Fig. 3: Flowchart of feature extract procedure

TABLE I: Model parameters (Bern-Barcelona Dataset)

	Input	Layer1	Layer2	Output	Loss function	Batch size	Epoch
Fully connected neural network (Keras)	48	32	32	2	mean squared error	675	10,000
PU learning (Chainer)	48	64	32	1	logistic	800	2,000

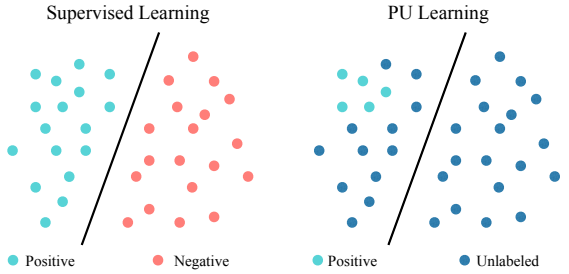

Fig. 4: Illustration of PU learning

A. Bern-Barcelona Dataset

In this dataset, we have 7,500 focal signals and 7,500 non-focal signals. Note that because Bern-Barcelona dataset is processed by the bandpass filter between 0.5 and 150 Hz, the frequency selection of bandpass are as follows: Delta (0.5-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), Beta (13-30 Hz), Gamma (30-80 Hz) and Ripple (80-150 Hz). We randomly choose 90% data samples as training data and 10% samples as test data when applying fully connected neural network. In PU learning, 14% focal samples are randomly selected as labeled data, while the rest of samples are selected as unlabeled data. Each experiment is performed by 10 times and the averaged results are provided.

The parameters of the model are manually chosen and shown in Table I, and the classification results are shown in Table III. The aim of the study is to use as small amount of labeled data as possible. The performances obtained by using different proportions of labeled data are shown in Table. IV.

B. Juntendo Database

In this dataset, there are 1,080 focal signals and 1,080 non-focal signals. We randomly select 90% smaples as training data and 10% samples as test data when applying three layers neural network. In PU learning, 14% focal samples are selected as labeled data, while the rest samples are selected as unlabeled data. The parameters of the model are manually chosen and shown in Table II. The experiments are performed by 10 times, then the averaged results are given in Table V. To investigate how many labeled samples can be reduced by using PU learning, the averaged performances obtained by different proportions of labeled data are shown in Table. VI. From the experimental results, the PU learning method uses a small performance loss, which in turn brings about a significant reduction in the marking workload.

IV. Conclusion

In this paper, we propose a novel approach for the classification of focal/non-focal iEEG signals. The feature extraction is performed by seven bandpass filters and eight entropy measurements. Then, our method is applied for classification as compared to the standard deep neural network. Our main contribution is to formulate the epileptic focus localization problem under the PU learning framework, which can significantly reduce the necessary number of labeled training samples. Therefore, the proposed approach is more practical than the popular supervised learning methods, especially when

TABLE II: Model parameters (Juntendo Dataset)

	Input	Layer1	Layer2	Output	Loss function	Batch size	Epoch
Fully connected neural network (Keras)	56	64	32	2	softsign	50	10,000
PU learning (Chainer)	56	64	32	1	logistic	800	2,000

TABLE III: Classification performance (Bern-Barcelona Dataset)

	Fully connected neural network	PU Learning
Accuracy (%)		
Mean (Std)	81.5 (0.269)	77.3 (0.568)

TABLE IV: Accuracies obtained by using different proportions of labeled data (Bern-Barcelona Dataset)

	6%	8%	10%	12%	14%
Accuracy (%)	74.9	75.2	76.4	76.6	77.3

TABLE V: Classification performance (Juntendo dataset)

	Fully connected neural network	PU Learning
Accuracy (%)		
Mean (Std)	94.5 (1.70)	88.5 (2.28)

TABLE VI: Accuracis obtained by using different proportions of labeled data (Juntendo Dataset)

	6%	8%	10%	12%	14%
Accuracy (%)	83.2	84.2	85.1	86.5	88.5

the labeling task is difficult such as the annotations of the epileptic focal. Because the accuracy of the PU learning method is somewhat lower than that of supervised learning, future work will focus on improving the accuracy of the PU learning method and approaching supervised learning as much as possible.

ACKNOWLEDGMENTS

This work was supported by JST CREST Grant Number JPMJCR1784, JSPS KAKENHI (Grant No. 17K00326 and 18K04178) and NSFC China (Grant No. 61773129).

REFERENCES

[1] R. S. Fisher, C. Acevedo, A. Arzimanoglou, A. Bogacz, J. H. Cross, C. E. Elger, J. Engel, L. Forsgren, J. A. French, M. Glynn *et al.*, "ILAE official report: a practical clinical definition of epilepsy," *Epilepsia*, vol. 55, no. 4, pp. 475–482, 2014.

[2] Q. Liu, Y. F. Chen, S. Z. Fan, M. F. Abbod, and J. S. Shieh, "A comparison of five different algorithms for EEG signal analysis in artifacts rejection for monitoring depth of anesthesia," *Biomedical Signal Processing and Control*, vol. 25, pp. 24–34, 2016.

[3] F. D. De Moraes and D. A. Callegari, "Automated detection of interictal spikes in EEG: A literature review," *Clin Neurophysiol*, pp. 1095–1103, 2014.

[4] R. Sharma, R. B. Pachori, and U. R. Acharya, "An integrated index for the identification of focal electroencephalogram signals using discrete wavelet transform and entropy measures," *Entropy*, vol. 17, no. 8, pp. 5218–5240, 2015.

[5] T. Itakura and T. Tanaka, "Epileptic focus localization based on bivariate empirical mode decomposition and entropy," *Asia Pacific Signal and Information Processing Association Annual Summit and Conference*, pp. 1426–1429, 2017.

[6] R. Sharma, R. B. Pachori, and U. R. Acharya, "Application of entropy measures on intrinsic mode functions for the automated identification of focal electroencephalogram signals," *Entropy*, vol. 17, no. 2, pp. 669–691, 2015.

[7] T. Itakura, I. Shintaro, T. Tanaka, and S. Hidenori, "Effective frequency bands and features for epileptic focus detectionfrom interictal electrocorticogram," *TECHNICAL REPORT OF IEICE*, pp. 311–316, 2018.

[8] R. G. Andrzejak, K. Schindler, and C. Rummel, "Nonrandomness, nonlinear dependence, and nonstationarity of electroencephalographic recordings from epilepsy patients," *Physical Review E*, vol. 86, no. 4, p. 046206, 2012.

[9] N. Kannathal, M. L. Choo, U. R. Acharya, and P. Sadasivan, "Entropies for detection of epilepsy in EEG," *Computer Methods and Programs in Biomedicine*, vol. 80, no. 3, pp. 187–194, 2005.

[10] J. Chen and G. Li, "Tsallis wavelet entropy and its application in power signal analysis," *Entropy*, vol. 16, no. 6, pp. 3009–3025, 2014.

[11] C. L. Nikias and J. M. Mendel, "Signal processing with higher-order spectra," *IEEE Signal Processing Magazine*, vol. 10, no. 3, pp. 10–37, 1993.

[12] S. M. Pincus, "Approximate entropy as a measure of system complexity," *Proceedings of the National Academy of Sciences*, vol. 88, no. 6, pp. 2297–2301, 1991.

[13] J. S. Richman and J. R. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy," *American Journal of Physiology Heart and Circulatory Physiology*, vol. 278, no. 6, pp. H2039–H2049, 2000.

[14] C. Bandt and B. Pompe, "Permutation entropy: a natural complexity measure for time series," *Physical Review Letters*, vol. 88, no. 17, p. 174102, 2002.

[15] A. Blum and T. Mitchell, "Combining labeled and unlabeled data with co-training," *Proceedings of the Eleventh Annual Conference on Computational Learning Theory*, pp. 92–100, 1998.

[16] B. Liu, W. S. Lee, P. S. Yu, and X. Li, "Partially supervised classification of text documents," *International Conference on Machine Learning*, vol. 2, pp. 387–394, 2002.

[17] X. Li and B. Liu, "Learning to classify texts using positive and unlabeled data," *International Joint Conference on Artificial Intelligence*, pp. 587–592, 2003.

[18] B. Liu, Y. Dai, X. Li, W. S. Lee, and P. S. Yu, "Building text classifiers using positive and unlabeled examples," *International Conference on Data Mining*, pp. 179–186, 2003.

[19] C. Elkan and K. Noto, "Learning classifiers from only positive and unlabeled data," *International Conference on Knowledge Discovery and Data Mining*, pp. 213–220, 2008.

[20] W. S. Lee and B. Liu, "Learning with positive and unlabeled examples using weighted logistic regression," *International Conference on Machine Learning*, pp. 448–455, 2003.

[21] M. C. du Plessis, G. Niu, and M. Sugiyama, "Analysis of learning from positive and unlabeled data," *Advances in Neural Information Processing Systems*, pp. 703–711, 2014.

[22] M. Du Plessis, G. Niu, and M. Sugiyama, "Convex formulation for learning from positive and unlabeled data," *International Conference on Machine Learning*, pp. 1386–1394, 2015.

[23] R. Kiryo, G. Niu, M. C. du Plessis, and M. Sugiyama, "Positive-unlabeled learning with non-negative risk estimator," *Advances in Neural Information Processing Systems*, pp. 1674–1684, 2017.