Semi-supervised Multiple Instance Learning using Variational Auto-Encoders

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Abstract

We consider the multiple-instance learning (MIL) paradigm, which is a special case of supervised learning where training instances are grouped into bags. In MIL, the hidden instance labels do not have to be the same as the label of the comprising bag. On the other hand, the hybrid modelling approach is known to possess advantages basically due to the smooth consolidation of both discriminative and generative components. In this paper, we investigate whether we can get the best of both worlds (MIL and hybrid modelling), especially in a semi-supervised learning (SSL) setting. We first integrate a variational autoencoder (VAE), which is a powerful deep generative model, with an attention-based MIL classifier, then evaluate the performance of the resulting model in SSL. We assess the proposed approach on an established benchmark as well as a real-world medical dataset.

1 Introduction

In the standard form of supervised learning, it is assumed that the learner encounters training data in a flat form where each instance, e.g., an image, belongs to a class (category). However, another setting which can be more practical in representing many real-world applications is multiple-instance learning (MIL), where training instances are grouped together into bags. In MIL, both bags and instances have labels, but an instance within a bag may have a different label from that of the bag. Only the bag label is available for learning since instance labels are not observed. Several applications can be cast as MIL problems, e.g., in medical imaging [Quellec et al., 2017] and computational biology [Dietterich et al., 1997].

The principal goal of MIL is to learn a model which can predict the bag label. This corresponds to the molecule binding property in the above example or to the all-important medical diagnosis in medical imaging applications. Nonetheless, inferring which instances are the most influential in predicting the bag label is of major importance due to several reasons including interpretability of the obtained prediction (especially in medical diagnosis) and related issues like GDPR (General Data Protection Regulation) which forces the right to understand in sensitive applications like self-driving cars and medical applications.

In this work, we investigate how the MIL framework fares in the semi-supervised learning paradigm (SSL, Zhu et al., 2003, Chapelle et al., 2006, Kingma et al., 2014, Siddharth et al., 2017). In SSL, the data presented to the learner typically consists of a few labeled examples as well as numerous unlabeled examples. The main goal of a semi-supervised learner is to utilize the unlabeled data in order to improve the model's performance on the supervised subset of the data. In case of the SSL MIL setting, the supervision is at the bag level. This means that the learner encounters both labeled and unlabeled bags.

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To deal with both the labeled and unlabeled data, we propose to learn a joint distribution over instances and a bag label within the hybrid modeling framework. Hybrid models are known to combine the advantages of (standard supervised) discriminative models with those of generative models [Jaakkola and Haussler, 1999, Tulyakov et al., 2017, Nalisnick et al., 2019]. Hybrid models have also been exploited in other frameworks including semi-supervised learning [Ilse et al., 2020, Nalisnick et al., 2019] and anomaly detection [Maaloe et al., 2019, Liu and Abbeel, 2020]. In this work, we propose an MIL framework which leverages the prowess of hybrid models so that they can excel in problems and applications possessing the bag-instance nature modelled by MIL. We build our modelling on top of the seminal attention-based deep MIL classifier [Ilse et al., 2018], mainly due to its permutation-invariant characteristics and its ability to give instance weights which can be interpreted as the contributions of each instance to the bag label. As a result, we formulate a latent variable model that could be seen as a Variational Auto-Encoder (VAE, Kingma and Welling, 2014, Rezende et al., 2014) for instances and a classifier that is fed with the outputs of the VAE's encoder. We evaluate the SSL performance of the proposed framework on a common benchmark and a real-world medical data.

As such, our main contributions can be summarized as follows: (1) Integrating an attention-based Deep MIL classifier with a deep generative model in the form of a VAE. (2) Developing an SSL framework based on the proposed hybrid MIL approach. (3) Evaluating the proposed hybrid approach on the semi-supervised MIL scenario and comparing it with baselines on two datasets (MNIST-BAGS, COLON-CANCER).

2 Methodology

2.1 Multiple-Instance Learning

In standard binary classification, the main goal is to establish a model which predicts the target variable $y \in \{0, 1\}$ for a data instance $\mathbf{x} \in \mathbb{R}^D$. On the other hand, each data sample in an MIL paradigm comes in the form of a bag of unordered and independent[1] instances $X = \{\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_K\}$, where the number of instances, referred to as K can differ for different bags. An MIL model must learn to predict the bag label Y, which is observed for the training data instances. In addition, there are also instance labels $y_1, y_2, \ldots, y_K$ which are all hidden even for the training data. The standard MIL rule on how to infer the bag label Y given its instance labels $y_1, y_2, \ldots, y_K$ can be expressed as follows:

$$Y = \begin{cases} 0, & \text{iff } \sum_k y_k = 0, \\ 1, & \text{otherwise.} \end{cases} \tag{1}$$

The MIL model we develop is trained by optimizing the log-likelihood (LL) function where the bag label is distributed according to a Bernoulli distribution $\theta(X) \in [0, 1]$, which depicts the probability $Y = 1$ given a bag X of instances. Also note that, since we assume bags of unordered and independent instances, the bag probability $\theta(X)$ must be permutation-invariant.

We pursue a three-step approach to predict bag labels, in which: (1) instances $\mathbf{x}_k$ are first transformed into a low-dimensional representation $\mathbf{z}_k = f_\psi(\mathbf{x}_k)$, (2) a combination of the transformed instances is formed via a permutation-invariant function (referred to as the MIL pooling), and (3) in order to form a bag representation, another transformation is applied over the combined instances, after which a classifier $\theta(X)$ is used for the resulting bag representation. We adopt a deep neural network to parameterize all the transformations. Thus, the whole model can be optimized in an end-to-end fashion via backpropagation.

2.2 Hybrid MIL

Joint distribution As mentioned earlier, we assume that instances within a bag X are identically and independently distribution. This assumption is crucial in our methodology. Further, we are interested in calculating the joint distribution over X and Y given the number of points in the bag X,

[1] We refer to the standard MIL case which assumes independence among instances within a bag. Nonetheless, there are a few works which study MIL settings where instances within a bag do not follow the IID assumption, e.g. [Zhou et al., 2009, Zhang, 2021]

$p(X, Y|K)$. Moreover, we consider the following generative model with shared latent variables:

$$p(X, Y|K) = \int p(Y, Z, X|K)\,\mathrm{d}Z \tag{2}$$

$$= \int p(Y|Z, X)p(X, Z|K)\,\mathrm{d}Z \tag{3}$$

$$= \int p(Y|Z)p(X|Z, K)p(Z|K)\,\mathrm{d}Z \tag{4}$$

$$\overset{iid}{=} \int p(Y|Z)\left(\prod_{k=1}^{K} p(\mathbf{x}_k|\mathbf{z}_k)p(\mathbf{z}_k)\right)\mathrm{d}Z, \tag{5}$$

where $Z = \{\mathbf{z}_1, \mathbf{z}_2, \ldots, \mathbf{z}_K\}$.

Variational inference We parameterize these distributions using neural networks, thus, calculating the integral becomes analytically intractable. In order to overcome this issue, we propose to use variational inference which allows calculating the lower bound to the logarithm of the joint distribution (the ELBO). Considering the following family of variational posteriors $q_\phi(Z|X, K) = \prod_{k=1}^{K} q_\phi(\mathbf{z}_k|\mathbf{x}_k)$ yields:

$$\log p_\vartheta(X, Y|K) = \log \int p_\vartheta(X, Y, Z|K)\frac{q_\phi(Z|X, K)}{q_\phi(Z|X, K)}\,\mathrm{d}Z \tag{6}$$

$$\geq \mathbb{E}_{q_\phi(Z|X)}\left[\log p_\vartheta(Y|Z) + \sum_{k=1}^{K}\Big(\log p_\vartheta(\mathbf{x}_k|\mathbf{z}_k) + \log p_\vartheta(\mathbf{z}_k) - \log q_\phi(\mathbf{z}_k|\mathbf{x}_k)\Big)\right] \tag{7}$$

$$\overset{df}{=} -\mathcal{L}(X, Y, K|\vartheta, \phi) \tag{8}$$

Notice that in the ELBO we have a component for the classification of a bag, $\log p(Y|Z)$, and a sum of objectives for each object in the bag X that conincide with the formulation of Variational Auto-Encoders [Kingma and Welling, 2014, Rezende et al., 2014].

Semi-supervised learning Since the ELBO consists of a sum of two objectives, namely, one for the classifier and one for the marginal over objects, the proposed approach is well-suited for semi-supervised learning. Let us denote the part with X as follows:

$$\mathcal{U}(X, K|\vartheta, \phi) \overset{df}{=} -\mathbb{E}_{q_\phi(Z|X)}\left[\sum_{k=1}^{K}\Big(\log p_\vartheta(\mathbf{x}_k|\mathbf{z}_k) + \log p_\vartheta(\mathbf{z}_k) - \log q_\phi(\mathbf{z}_k|\mathbf{x}_k)\Big)\right]. \tag{9}$$

For two given sources of data, namely, laballed data $(X, Y) \sim p_l(X, Y)$, and unlabelled data $X \sim p_u(X)$, we can formulate a joint learning objective by minimizing the combination of $\mathcal{L}(X, Y, K|\vartheta, \phi)$ and $\mathcal{U}(X, K|\vartheta, \phi)$. However, typically we have more unlabelled data, therefore we consider a weighted objective:

$$\mathcal{J}(\vartheta, \phi) = \alpha \cdot \sum_{(X,Y)\sim p_l} \mathcal{L}(X, Y, K|\vartheta, \phi) + \sum_{X\sim p_u} \mathcal{U}(X, K|\vartheta, \phi), \tag{10}$$

where $\alpha > 0$. This approach is known as *hybrid modeling* [Lasserre et al., 2006].

Modeling $p(Y|Z)$ In this paper, we pursue an attention-based MIL pooling approach for modeling $p(Y|Z)$ due to several reasons: Attention-based MIL pooling is more flexible, adaptive, and more trainable than the max and mean pooling operators. It is also more interpretable due to the data-driven adjustment of instance weights according to the task and data at hand, which can potentially provide instance scores signifying the most relevant instances w.r.t. the bag label prediction. Attention-based pooling is depicted in the form of a weighted averaging with learnable parameters. To ensure invariance to the size (i.e. number of instances) of a bag, the weights are constrained to sum up to 1.

Assuming a bag of K instance representation embeddings $Z = \{\mathbf{z}_1, \ldots, \mathbf{z}_K\}$, the MIL pooling is expressed as:

$$\mathbf{h} = \sum_{k=1}^{K} a_k \mathbf{z}_k, \tag{11}$$

where:

$$a_k = \frac{\exp\{\mathbf{w}^\top \big(\tanh\big(\mathbf{V}\mathbf{z}_k^\top\big) \odot \mathrm{sigm}\big(\mathbf{U}\mathbf{z}_k^\top\big)\big)\}}{\sum_{j=1}^{K} \exp\{\mathbf{w}^\top \big(\tanh\big(\mathbf{V}\mathbf{z}_j^\top\big) \odot \mathrm{sigm}\big(\mathbf{U}\mathbf{z}_j^\top\big)\big)\}}, \tag{12}$$

where $\mathbf{w} \in \mathbb{R}^{L\times 1}$, $\mathbf{V} \in \mathbb{R}^{L\times M}$ and $\mathbf{U} \in \mathbb{R}^{L\times M}$ are parameters, and $\tanh(\cdot)$ is an element-wise hyperbolic tangent nonlinearity. Element-wise multiplication is depicted by $\odot$, and $\mathrm{sigm}(\cdot)$ refers to the sigmoid nonlinearity which grants the adoption of a gating mechanism, potentially avoiding some troublesome linearity issues associated with $\tanh(\cdot)$ [Ilse et al., 2018].

Eventually, the classifier works as follows:

1. X is transformed to Z through a shared stochastic encoder $q_\phi(Z|X, K)$, i.e., we calculate a sample $Z \sim q_\phi(Z|X, K)$.
2. An embedding $\mathbf{h}$ is calculated trough the attention-based MIL pooling operator (see Eq. 11) for given Z.
3. A neural network is used to calculate probabilities of class labels, $\theta(\mathbf{h})$.

3 Experiments

We quantitatively and qualitatively evaluate the proposed framework, which we refer to as semi-supervised multiple-instance learning variational autoencoder (ssMILVAE). The conducted experiments mainly address the following issues: (i) To assess the (accuracy) performance of the proposed ssMILVAE in the SSL paradigm, and (ii) to gauge the degree of interpretability granted by ssMILVAE and whether the learned instance weights can provide information on the contributions of each instance to the bag label prediction.

We assess ssMILVAE on two datasets, MNIST-BAGS which is an MNIST-based image dataset, and COLON CANCER which is a real-world histopathology dataset. We use 10-fold cross-validation and repeat each experiment five times. To compare on common ground, we follow most of the settings and modelling choices pursued by Ilse et al. [2018]. We refer to the latter method here as AD-MIL. The MIL pooling layers are located right below the top layer of the model. In addition to the classification accuracy, we compare the bag level performance based on: recall (true positive rate), the area under the receiver operating characteristic curve (AUC) and (bag) classification accuracy. All the experiments have been run for 100 epochs. Adam [Kingma and Ba, 2015] is the optimized used, with values of β_1 and β_2 set equal to 0.9 and 0.999, respectively. Weights are initialized according to [He et al., 2015]. The hyperparameter α (i.e., the weighting between the labelled objective and the unlabelled objective) was determined through the model selection on the validation set.

3.1 MNIST-BAGS

MNIST-BAGS is based on the well-known MNIST image data. We sample images from the MNIST training (test) set to form training (test) bags, respectively. Each bag consists of a random number of 28×28 greyscale handwritten MNIST images. Number of images within a bag is Gaussian distributed where the closest integer value is the chosen bag size. Since the number '9' can possibly be confused with '7' and '4', we rate a bag as positive if it contains at least one image of the digit '9'.

The ROC and accuracy results are displayed in Figures 1. The results demonstrate the supremacy of the proposed ssMILVAE when the learner encounters a small number of labeled bags. The performance of ssMILVAE is nearly equalled by AD-MIL with a larger number of labeled bags.

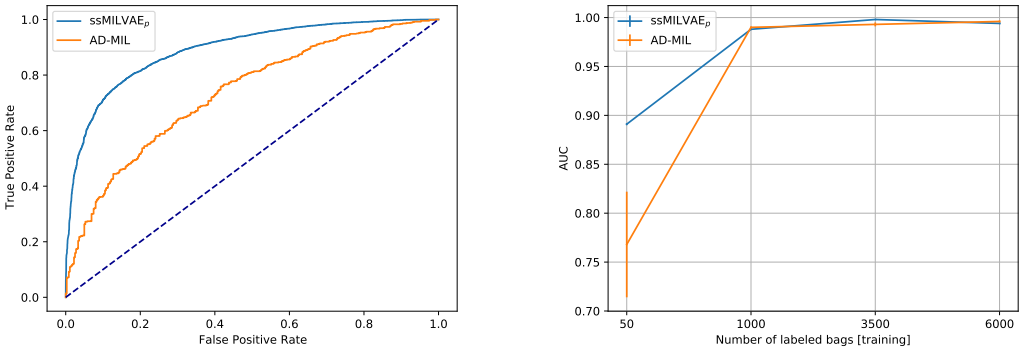
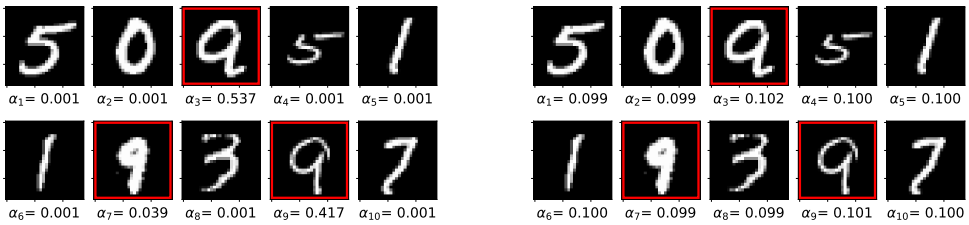


Figure 1: A comparison between ssMILVAE and AD-MIL. **A:** The ROC curve results for a bag size of 10 instances on the MNIST-BAGS dataset. **B:** The bag AUC results for 10-instance bags on the MNIST-BAGS dataset.

We next evaluate the attention mechanism of the proposed ssMILVAE algorithm on the MNIST-BAGS dataset, and compare it with the seminal AD-MIL approach. We compare the two algorithms based on a rather limited number of labeled bags, which is 50 bags. The bags displayed in Figure 4 have been correctly classified by both algorithms and not cherry-picked. The proposed ssMILVAE is capable of assigning higher weights to the positive instances than AD-MIL. This suggests that ssMILVAE may provide more *interpretable* bag label predictions than AD-MIL, when trained on a limited number of labeled bags, since the instance weights convey the relevance of the respective instances for the bag labeling decision.



(a) ssMILVAE (b) AD-MIL

Figure 2: Evaluation of the attention mechanism of the proposed ssMILVAE algorithm compared to that of AD-MIL, tested on bags containing multiple positive ('9') instances from the MNIST-BAGS dataset.

3.2 COLON CANCER

The COLON CANCER dataset consists of real-world histopathology data [Sirinukunwattana et al., 2016]. The data contains cancerous regions in hematoxylin and eosin (H&E) stained whole-slide images. There are a total of 22,444 nuclei labeled as epithelial, inflammatory, fibroblast or miscellaneous. It consists of 100 H&E images originating from a variety of tissue appearances from healthy and malignant regions [Ilse et al., 2018]. Each bag consists of 27 $\times$ 27 patches. A bag is labeled as positive if it contains at least one epithelial nuclei. Colon cancer clinically originates from epithelial cells, and this is why epithelial nuclei are very informative about the diagnosis here.

The accuracy results for experiments on the COLON CANCER dataset are displayed in Figure 3. We experiment with the following number of labeled training bags: 22, 92 and 162. The proposed ssMILVAE algorithm is more accurate when trained on a small number of training bags. When the number of available labeled training bags increases, AD-MIL begins to outperform ssMILVAE.

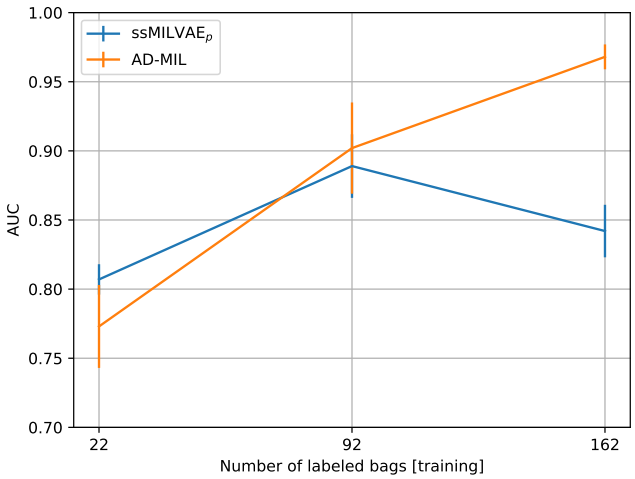


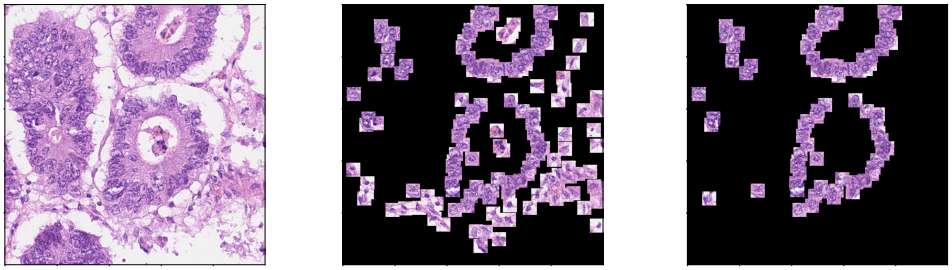
Figure 3: The bag AUC results on the COLON CANCER dataset for the proposed ssMILVAE and AD-MIL given a small number of labeled training bags.

Regarding the attention mechanism, we compare the proposed ssMILVAE with AD-MIL in terms of the resulting regions of interest (ROIs), which are of paramount importance in medical diagnosis. The raw histopathological image is displayed in Figure 4a. The histopathological image is split into smaller patches containing single cells. A heatmap is generated by multiplying cell images by their respective attention weights. The attention weights are then rescaled using $a' = \frac{a_k - min(a)}{max(a) - min(a)}$. As can be noticed in Figure 4d, the proposed attention mechanism by ssMILVAE achieves a much better outcome in spotting the relevant cells compared to AD-MIL. As such, the attention mechanism of the proposed ssMILVAE provides more interpretable predictions by identifying the key patches responsible for the diagnosis.

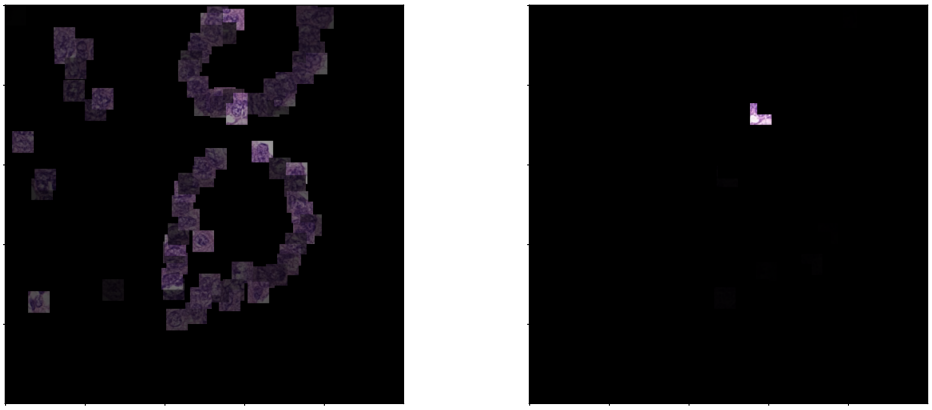
4 Conclusion

In this paper, we have presented an extension of the MIL classification problem to learning a joint distribution in the semi-supervised setting. We have proposed a latent variable model for the MIL generative model with a shared parameterization between the classifier and the unsupervised part. In the experiments, we have shown that the proposed approach is beneficial in cases with a limited number of labeled data.

In many applications, (especially in the medical domain), it is difficult to obtain huge sizes of labeled cases, and in such cases ssMILVAE seems to represent a recommended choice due to its ability to learn from limited numbers of labeled bags (medical cases). Moreover, the attention mechanism allows assisting a human expert (e.g., a physician) in interpreting results.



(a) Raw image (b) All cells (c) The ground-truth relevant cells



(d) Attention mechanism of the proposed ssMILVAE. (e) Attention mechanism of AD-MIL.

Figure 4: Evaluation of the attention mechanism of the proposed ssMILVAE algorithm compared to that of AD-MIL, tested on the COLON CANCER dataset. Compared to AD-MIL, ssMILVAE assigns significantly higher weights to most of the relevant cells.

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