

MULTIPLE INSTANCE LEARNING VIA ITERATIVE SELF-PACED SUPERVISED CONTRASTIVE LEARNING

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ABSTRACT

Learning representations for individual instances when only bag-level labels are available is a fundamental challenge in multiple instance learning (MIL). Recent works have shown promising results using contrastive self-supervised learning (CSSL), which learns to push apart representations corresponding to two different randomly-selected instances. Unfortunately, in real-world applications such as medical image classification, there is often class imbalance, so randomly-selected instances mostly belong to the same majority class, which precludes CSSL from learning inter-class differences. To address this issue, we propose a novel framework, Iterative Self-paced Supervised Contrastive Learning for MIL Representations (*ItS2CLR*), which improves the learned representation by exploiting instance-level pseudo labels derived from the bag-level labels. The framework employs a novel self-paced sampling strategy to ensure the accuracy of pseudo labels. We evaluate *ItS2CLR* on three medical datasets, showing that it improves the quality of instance-level pseudo labels and representations, and outperforms existing MIL methods in terms of both bag and instance level accuracy.

1 INTRODUCTION

The goal of multiple instance learning (MIL) is to perform classification on data that is arranged in *bags* of instances. Each instance is either positive or negative, but these instance-level labels are not available during training; only bag-level labels are available. A bag is labeled as positive if *any* of the instances in it are positive, and negative otherwise. An important application of MIL is cancer diagnosis from histopathology slides. Each slide is divided into hundreds or thousands of tiles but typically only slide-level labels are available (Courtiol et al., 2018; Campanella et al., 2019; Li et al., 2021; Chen and Krishnan, 2022; Zhang et al., 2022; Lu et al., 2021).

Histopathology slides are typically very large, in the order of gigapixels (the resolution of a typical slide can be as high as $10^5 \times 10^5$), so end-to-end training of deep neural networks is typically infeasible due to memory limitations of GPU hardware. Consequently, state-of-the-art approaches (Campanella et al., 2019; Li et al., 2021; Zhang et al., 2022; Lu et al., 2021; Shao et al., 2021) utilize a two-stage learning pipeline: (1) a feature-extraction stage where each instance is mapped to a representation which summarizes its content, and (2) an aggregation stage where the representations extracted from all instances in a bag are combined to produce a bag-level prediction (Figure 1). Notably, our results indicate that even in rare settings where end-to-end training is possible, this pipeline is still superior (see Section 4.3).

In this work, we focus on a fundamental challenge in MIL: how to train the feature extractor. Currently, there are three main strategies to perform feature-extraction, which have significant shortcomings. (1) Pretraining on a large natural image dataset such as ImageNet (Shao et al., 2021; Lu et al., 2021) is problematic for medical applications because features learned from natural images may generalize poorly to other domains (Lu et al., 2020). (2) Supervised training using bag-level labels as instance-level labels is effective if positive bags contain mostly positive instances (Lerousseau et al., 2020; Xu et al., 2019; Chikontwe et al., 2020), but in many medical datasets this is not the case (Bejnordi et al., 2017; Li et al., 2021). (3) Contrastive self-supervised learning (CSSL) outperforms prior methods (Li et al., 2021; Ciga et al., 2022), but is not as effective in settings with heavy class imbalance, which are of crucial importance in medicine. CSSL operates by pushing apart the representations of different randomly selected instances. When positive bags contain

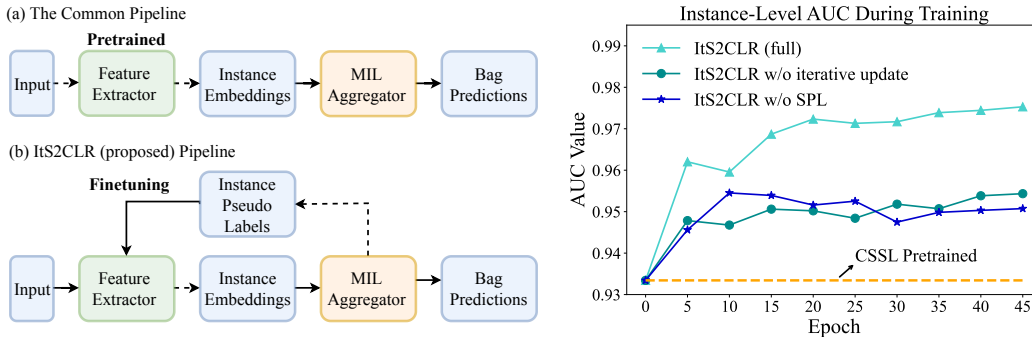


Figure 1: **Left:** (a) Commonly used deep MIL models first pretrain a feature extractor and then train an aggregator that maps the representations to a bag-level prediction. (b) Our proposed framework, ItS2CLR, uses instance-level pseudo labels obtained from the aggregator to finetune the feature extractor. ItS2CLR updates the features iteratively based on the pseudo label of a subset of instances selected according to a self-paced learning (SPL) strategy. **Right:** On a benchmark dataset (Came-lyon16 Bejnordi et al. (2017)), the iterative finetuning process gradually improves the instance-level AUC during training, which results in more accurate pseudo labels. Both the iterative updates and SPL are important to achieve this.

mostly negative instances, CSSL training ends up pushing apart negative instances from each other, which precludes it from learning features that distinguish positive samples from the negative ones (Figure 2). We discuss this finding in Section 2.

Our goal is to address the shortcomings of current feature-extraction methods. We build upon several key insights. First, it is possible to extract instance-level pseudo labels from trained MIL models, which are more accurate than assigning the bag-level labels to all instances within a positive bag. Second, we can use the pseudo labels to finetune the feature extractor, improving the instance-level representations. Third, these improved representations result in improved bag-level classification and more accurate instance-level pseudo labels. These observations are utilized in our proposed framework, Iterative Self-Paced Supervised Contrastive Learning for MIL Representation (ItS2CLR), as illustrated in Figure 1. After initializing the features with CSSL, we iteratively improve them via supervised contrastive learning (Khosla et al., 2020) using pseudo labels inferred by the aggregator. This feature refinement utilizes pseudo labels sampled according to a novel self-paced strategy, which ensures that they are sufficiently accurate (see Section 3.2). In summary, our contributions are the following:

1. We propose ItS2CLR – a novel MIL framework where instance features are iteratively improved using pseudo labels extracted from the MIL aggregator. The framework combines supervised contrastive learning with a self-paced sampling scheme to ensure that pseudo labels are accurate.
2. We demonstrate that the proposed approach outperforms existing MIL methods in terms of bag- and instance-level accuracy on three real-world medical datasets relevant to cancer diagnosis: two histopathology datasets and a breast ultrasound dataset. It also outperforms alternative finetuning methods, such as instance-level cross-entropy minimization and end-to-end training.
3. In a series of controlled experiments, we show that ItS2CLR is effective when applied to different feature-extraction architectures and when combined with different aggregators.

2 CSSL MAY NOT LEARN DISCRIMINATIVE FEATURES IN MIL

Recent MIL approaches use contrastive self-supervised learning (CSSL) to train the feature extractor (Li et al., 2021; Saillard et al., 2021; Rymarczyk et al., 2021). In this section, we show that CSSL has a crucial limitation in realistic MIL settings, which precludes it from learning discriminative features. CSSL aims to learn a representation space where samples from the same class are close to each other, and samples from different classes are far from each other, without access to class labels. This is achieved by minimizing the InfoNCE loss (Oord et al., 2018).

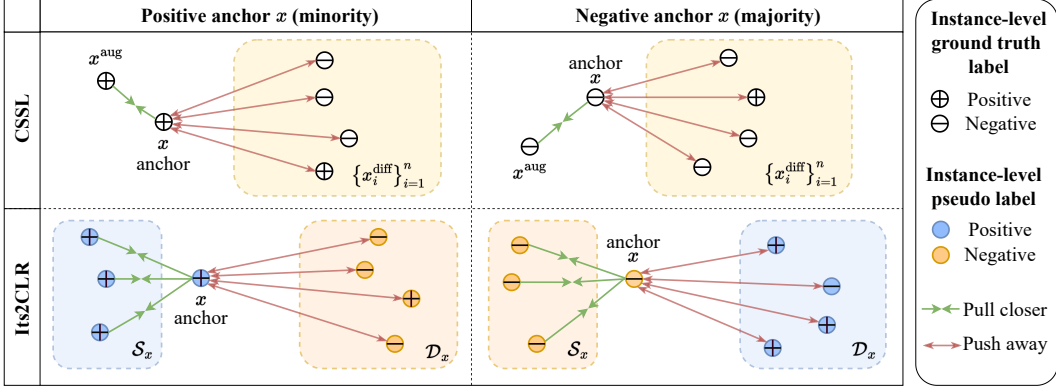


Figure 2: **Top:** In contrastive self-supervised learning (CSSL), the representation of an instance x is pulled closer to its random augmentation x^{aug} and pushed away from the representations of other randomly selected instances $\{x_i^{\text{diff}}\}_{i=1}^n$. In many MIL datasets relevant to medical diagnosis, most instances are negative, so CSSL mostly pushes apart representations of negative instances (right). **Bottom:** Our proposed framework Its2CLR applies the supervised contrastive learning approach described in Section 3.1. Instance-level pseudo labels are used to build a set of positive pairs \mathcal{S}_x and a set of negative pairs \mathcal{D}_x corresponding to x . The representation of an instance x is pulled closer to those in \mathcal{S}_x and pushed away from those in \mathcal{D}_x . The set of pseudo-labels is built iteratively following the self-paced sampling strategy in Section 3.2.

$$\mathcal{L}_{\text{CSSL}} = \mathbb{E}_{x, x^{\text{aug}}, \{x_i^{\text{diff}}\}_{i=1}^n} \left[-\log \frac{\exp(f_\psi(x) \cdot f_\psi(x^{\text{aug}})/\tau)}{\exp(f_\psi(x) \cdot f_\psi(x^{\text{aug}})/\tau) + \sum_{i=1}^n \exp(f_\psi(x) \cdot f_\psi(x_i^{\text{diff}})/\tau)} \right], \quad (1)$$

where $f_\psi = f \circ \psi$, in which $f: \mathbb{R}^m \rightarrow \mathbb{R}^d$ is the feature extractor mapping the input data to a representation, $\psi: \mathbb{R}^d \rightarrow \mathbb{R}^d$ is a projection head with a feed-forward network and ℓ_2 normalization, and τ is a temperature hyperparameter. The expectation is taken over samples $x \in \mathbb{R}^m$ drawn uniformly from the training set. Minimizing the loss brings the representation of an instance x closer to the representation of its random augmentation, x^{aug} , and pushes the representation of x away from the representations of n other examples $\{x_i^{\text{diff}}\}_{i=1}^n$ in the training set.

A key assumption in CSSL is that x belongs to a different class than most of the randomly-sampled examples $x_1^{\text{diff}}, \dots, x_n^{\text{diff}}$. This usually holds in standard classification datasets with many classes such as ImageNet (Deng et al., 2009), but *not in MIL tasks relevant to medical diagnosis*, where a majority of instances are negative (e.g. 95% in Camelyon16). Hence, most terms in the sum $\sum_{i=1}^n \exp(f_\psi(x) \cdot f_\psi(x_i^{\text{diff}})/\tau)$ in the loss in Equation 1 correspond to pairs of examples (x, x_i^{diff}) both belonging to the negative class. Therefore, minimizing the loss mostly pushes apart the representations of negative instances, as illustrated in the top panel of Figure 2. This is an example of *class collision* (Arora et al., 2019; Chuang et al., 2020), a general problem in CSSL, which has been shown to impair performance on downstream tasks (Ash et al., 2021; Zheng et al., 2021).

Class collision makes CSSL learn representations that are not discriminative between classes. In order to study this phenomenon, we report the average inter-class distances and intra-class deviations for representations learned by CSSL on Camelyon16 in Table 1. The inter-class distance reflects how far the instance representations from different classes are apart; the intra-class distance reflects the variation of instance representations within each class. As predicted, the intra-class deviation corresponding to the representations of negative instances learned by CSSL is large. Representations learned by Its2CLR have larger inter-class distance (more separated classes) and smaller intra-class deviation (less variance among instances belonging to the same class) than those learned by CSSL. This suggests that the features learned by Its2CLR are more discriminative, which is confirmed by the results in Section 4.

Note that using bag-level labels does not solve the problem of class collision. When x is negative, even if we select $\{x_i^{\text{diff}}\}_{i=1}^n$ from the positive bags in equation 1, most of the selected instances

Table 1: Quantitative analysis of instance-level features learned from Camelyon16 (Bejnordi et al., 2017). The inter-class distance is the ℓ_2 -distance between the representation mean of the positive instances and that of the negative instances. The intra-class deviation is the square root of the spectral norm of the covariance matrix of the features corresponding to each class. The spectral norm is the largest eigenvalue of the covariance matrix and is therefore equal to the variance in the direction of the greatest variance. Due to class collision among negative instances in CSSL (see Section 2), the intra-class deviation of the corresponding features is very large. In contrast, the features learned by the proposed framework ItS2CLR has smaller intra-class deviation among both negative and positive instances, and a larger inter-class distance.

	Training set			Test set		
	Inter-class distance	Intra-class deviation		Inter-class distance	Intra-class deviation	
		<i>pos</i>	<i>neg</i>		<i>pos</i>	<i>neg</i>
CSSL (SimCLR)	1.835	1.299	1.453	2.109	1.416	1.484
ItS2CLR (proposed)	2.376	1.176	0.805	2.432	1.215	0.847

will still be negative. Overcoming the class-collision problem requires explicitly detecting positive instances. This motivates our proposed framework, described in the following section.

3 MIL VIA ITERATIVE SELF-PACED SUPERVISED CONTRASTIVE LEARNING

Iterative Self-paced Supervised Contrastive Learning for MIL Representations (ItS2CLR) addresses the limitation of contrastive self-supervised learning (CSSL) described in Section 2. ItS2CLR relies on latent variables indicating whether each instance is positive or negative, which we call *instance-level pseudo labels*. To estimate pseudo labels, we use instance-level probabilities obtained from the MIL aggregator (we use the aggregator from DS-MIL (Li et al., 2021) but our framework is compatible with any aggregator that generates instance-level probabilities). The pseudo labels are obtained by binarizing the probabilities according to a threshold $\eta \in (0, 1)$, which is a hyperparameter.

ItS2CLR uses the pseudo labels to finetune the feature extractor (initialized using CSSL). In the spirit of iterative self-training techniques (Zhong et al., 2019; Wei et al., 2020; Liu et al., 2022), we alternate between refining the feature extractor, re-computing the pseudo labels, and training the aggregator, as described in Algorithm 1. A key challenge is that the pseudo labels are not completely accurate, especially at the beginning of the training process. To address the impact of incorrect pseudo labels, we apply a contrastive loss to finetune the feature extractor (see Section 3.1), where the contrastive pairs are selected according to a novel self-paced learning scheme (see Section 3.2). The right panel of Figure 1 shows that our approach iteratively improves the pseudo labels on the Camelyon16 dataset (Bejnordi et al., 2017). This finetuning only requires a modest increment in computational time (see Appendix A.3).

3.1 SUPERVISED CONTRASTIVE LEARNING WITH PSEUDO LABELS

To address the class collision problem described in Section 2, we leverage *supervised* contrastive learning (Pantazis et al., 2021; Dwibedi et al., 2021; Khosla et al., 2020) combined with the pseudo labels estimated by the aggregator. The goal is to learn discriminative representations by pulling together the representations corresponding to instances in the same class, and pushing apart those belong to instances of different classes. For each *anchor* instance x selected for contrastive learning, we collect a set \mathcal{S}_x believed to have the *same label* as x , and a set \mathcal{D}_x believed to have a *different label* to x . These sets are depicted in the bottom panel of Figure 2. The supervised contrastive loss corresponding to x is defined as:

$$\mathcal{L}_{\text{sup}}(x) = \frac{1}{|\mathcal{S}_x|} \sum_{x_s \in \mathcal{S}_x} -\log \frac{\exp(f_\psi(x) \cdot f_\psi(x_s)/\tau)}{\sum_{x_s \in \mathcal{S}_x} \exp(f_\psi(x_i) \cdot f_\psi(x_s)/\tau) + \sum_{x_d \in \mathcal{D}_x} \exp(f_\psi(x) \cdot f_\psi(x_d)/\tau)}. \quad (2)$$

In Section 3.2, we explain how to select x , \mathcal{S}_x and \mathcal{D}_x to ensure that the selected samples have high-quality pseudo labels.

A tempting alternative to supervised contrastive learning is to train the feature extractor on pseudo labels using standard cross-entropy loss. However, in Section 4.3 we show that this leads to sub-

Algorithm 1 Iterative Self-Paced Supervised Contrastive Learning (It2SCLR)

Require: Feature extractor f , projection head ψ , MIL aggregator g_ϕ , where ϕ is an instance classifier

Require: Bags $\{X_b\}_{b=1}^B$, bag-level labels $\{Y_b\}_{b=1}^B$

- 1: $f^{(0)} \leftarrow f_{\text{SSL}}$ ▷ Initialize f with CSSL-pretrained weights
- 2: **for** $t = 0$ to T **do**
- 3: $h_k^b \leftarrow f^{(t)}(x_k^b), \forall x_k^b \in X_b, \forall b$ ▷ Extract instance representation
- 4: $H_b \leftarrow \{h_k^b\}_{k=1}^{K_b}, \forall b$ ▷ Group instance embedding into bags
- 5: $g_\phi^{(t)} \leftarrow \text{Train with } \{H_b\}_{b=1}^B \text{ and } \{Y_b\}_{b=1}^B$ ▷ Train the aggregator
- 6: $\text{AUC}_{\text{val}}^{(t)} \leftarrow \text{bag-level AUC on the validation set}$
- 7: **if** $\text{AUC}_{\text{val}}^{(t)} \geq \max_{t' \leq t} \{\text{AUC}_{\text{val}}^{(t')}\}$ **then** ▷ If bag prediction improves
- 8: $\hat{y}_k^b \leftarrow \mathbb{1}_{\{\phi^{(t)}(h_k^b) > \eta\}}, \forall x_k^b \in X_b, \forall b$ ▷ Update instance pseudo labels
- 9: **end if**
- 10: $f_\psi^{(t+1)} \leftarrow \text{argmin}_{f_\psi} \mathcal{L}_{\text{sup}}(f_\psi^{(t)})$ ▷ Optimize feature extractor via Eq.(2)
- 11: **end for**

stantially worse performance in the downstream MIL classification task due to memorization of incorrect pseudo labels. On the contrary, we can leverage self-paced sampling to choose contrastive pairs with the most confident, even certain, pseudo labels for supervised contrastive learning.

3.2 SAMPLING VIA SELF-PACED LEARNING

A key challenge in It2SCLR is to improve the accuracy of instance-level pseudo labels without ground-truth labels. This is achieved by finetuning the feature extractor on a carefully-selected subset of instances. We select the anchor instance x and the corresponding sets \mathcal{S}_x and \mathcal{D}_x (defined in Section 3.1 and Figure 2) building upon two key insights: (1) The negative bags only contain negative instances. (2) The probabilities used to build the pseudo labels are indicative of their quality; instances with higher predicted probabilities usually have more accurate pseudo labels (Zou et al., 2018a; Liu et al., 2020; 2022).

Let $\mathcal{X}_{\text{neg}}^-$ denote all instances within the negative bags. By definition of MIL, we can safely assume that all instances in $\mathcal{X}_{\text{neg}}^-$ are negative. In contrast, positive bags contain both positive and negative instances. Let $\mathcal{X}_{\text{pos}}^+$ and $\mathcal{X}_{\text{pos}}^-$ denote the sets of instances in positive bags with positive and negative pseudo labels respectively. During an initial warm-up lasting $T_{\text{warm-up}}$ epochs, we sample anchor instances x only from $\mathcal{X}_{\text{neg}}^-$ to ensure that they are indeed all negative. For each such instance, \mathcal{S}_x is built by sampling instances from $\mathcal{X}_{\text{neg}}^-$, and \mathcal{D}_x is built by sampling from $\mathcal{X}_{\text{pos}}^+$.

After the warm-up phase, we start sampling anchor instances from $\mathcal{X}_{\text{pos}}^+$ and $\mathcal{X}_{\text{pos}}^-$. To ensure that these instances have accurate pseudo labels, we only consider the top- $r\%$ instances with the highest probabilities in each of these sets, which we call $\mathcal{X}_{\text{pos}}^+(r)$ and $\mathcal{X}_{\text{pos}}^-(r)$ respectively, as illustrated by Figure 5 (the ratio of positive-to-negative anchors is a fixed hyperparameter p_+). For each anchor x , the same-label set \mathcal{S}_x is sampled from $\mathcal{X}_{\text{pos}}^+(r)$ if x is positive and from $\mathcal{X}_{\text{neg}}^- \cup \mathcal{X}_{\text{pos}}^-(r)$ if x is negative. The different-label set \mathcal{D}_x is sampled from $\mathcal{X}_{\text{neg}}^- \cup \mathcal{X}_{\text{pos}}^+(r)$ if x is positive, and from $\mathcal{X}_{\text{pos}}^+(r)$ if x is negative.

To exploit the improvement of the instance representations during training, we gradually increase r to include more instances from positive bags, which can be interpreted as a self-paced *easy-to-hard* learning scheme (Kumar et al., 2010; Jiang et al., 2014; Zou et al., 2018b). Let t and T denote the current epoch, and the total number of epochs respectively. For $T_{\text{warmup}} < t \leq T$, we set:

$$r := r_0 + \alpha_r (t - T_{\text{warm-up}}), \text{ where } \alpha_r = (r_T - r_0)/(T - T_{\text{warm-up}}), \quad (3)$$

and r_0 and r_T are hyperparameters. Details on tuning these hyperparameters are provided in Appendix A.4. As demonstrated in the right panel of Figure 1 (see also Appendix B.1), this scheme indeed results in an improvement of the pseudo labels (and hence of the underlying representations).

Table 2: Bag-level AUC of Its2CLR and a two-stage baseline using a SimCLR feature extractor and a MIL aggregator. Both models use the same aggregator (see Appendix A.2 for more details). Its2CLR outperforms the baseline on all three datasets.

AUC ($\times 10^{-2}$)	Camelyon16	Breast Ultrasound	TCGA-LUAD mutation			
			EGFR	KRAS	STK11	TP53
SimCLR + Aggregator	85.38	80.79	67.51	68.79	70.40	62.15
Its2CLR	94.25	93.93	72.30	71.06	75.08	65.61

4 EXPERIMENTS

We evaluate Its2CLR on three MIL datasets described in Section 4.1. In Section 4.2 we show that Its2CLR consistently outperforms approaches that use CSSL feature-extraction by a substantial margin on all three datasets for different choices of aggregators. In Section 4.3 we show that Its2CLR outperforms alternative finetuning approaches based on cross-entropy loss minimization and end-to-end training across a wide range of settings where the prevalence of positive instances and bag size vary. In Section 4.4, we show that Its2CLR is able to improve features obtained from a variety of pretraining schemes and network architectures.

4.1 DATASETS

We evaluate the proposed framework on three cancer diagnosis tasks. When training our models, we select the model with the highest bag-level performance on the validation set and report the performance on a held-out test set. More information about the datasets, experimental setup, and implementation is provided in Appendix A.

Camelyon16 (Bejnordi et al., 2017) is a popular benchmark for MIL (Li et al., 2021; Shao et al., 2021; Zhang et al., 2022) where the goal is to detect breast-cancer metastasis in lymph node sections. It consists of 400 whole-slide histopathology images. Each whole slide image (WSI) corresponds to a bag with a binary label indicating the presence of cancer. Each WSI is divided into an average of 625 tiles at 5x magnification, which correspond to individual instances. The dataset also contains pixel-wise annotations indicating the presence of cancer, which can be used to derive ground-truth instance-level labels.

TCGA-LUAD is a dataset from The Cancer Genome Atlas (TCGA) (tcg), a landmark cancer genomics program, where the associated task is to detect genetic mutations in cancer cells. Detecting these mutations is important to determine treatment options for LUAD (Coudray et al., 2018; Fu et al., 2020). The data contains 800 labeled tumorous frozen WSIs from lung adenocarcinoma (LUAD). Each WSI is divided into an average of 633 tiles at 10x magnification corresponding to unlabeled instances.

The **Breast Ultrasound Dataset** contains 28,914 B-mode breast ultrasound exams (Shen et al., 2021a). The associated task is to detect breast cancer. Each exam contains between 4-70 images (18.8 images per exam on average) corresponding to individual instances, but only a bag-level label indicating the presence of cancer is available per exam. Additionally, a subset of images is annotated, which makes it possible to also evaluate instance-level performance. This dataset is imbalanced at the bag level: only 5,593 of 28,914 exams contain cancer.

4.2 COMPARISON WITH CONTRASTIVE SELF-SUPERVISED LEARNING

In this section, we compare the performance of Its2CLR to a baseline that performs feature-extraction via the CSSL method SimCLR (Chen et al., 2020). This approach has achieved state-of-the-art performance on multiple WSI datasets (Li et al., 2021). To ensure a fair comparison, we initialize the feature extractor in Its2CLR also using SimCLR. Table 2 shows that Its2CLR clearly outperforms the SimCLR baseline on all three datasets. The performance improvement is particularly significant in Camelyon16 where it achieves a bag-level AUC of 0.943, outperforming the baseline by an absolute margin of 8.87%. Its2CLR also outperforms an improved baseline reported by Li et al. (2021) with an AUC of 0.917, which uses higher resolution tiles than in our experiments (both 20x and 5x, as opposed to only 5x).

Table 3: Bag-level AUC on Camelyon16 for ItS2CLR and different baselines for five aggregators. We retrain each aggregator 5 times to report the mean and standard deviation (reported as a subscript). All feature extractors are initialized using SimCLR. Ground-truth and cross-entropy (CE) finetuning use ground-truth instance-level labels and pseudo labels to optimize the feature extractor respectively. We also include versions of ItS2CLR without iterative updates (w/o iter.), self-paced learning (w/o SPL) and both (w/o both), and a version of CE finetuning without iterative updates (w/o iter). See Appendix A.6 for a detailed description of the ablated models.

AUC ($\times 10^{-2}$)	SimCLR (CSSL)	Ground-truth finetuning*	CE finetuning		ItS2CLR			
			w/o iter.	iter.	w/o both	w/o iter.	w/o SPL	Full
Max pooling	86.69 _{1.09}	98.25 _{0.01}	85.48 _{0.24}	88.05 _{0.77}	85.38 _{0.31}	91.96 _{0.31}	90.85 _{0.76}	94.69 _{0.07}
Top-k pooling	85.39 _{1.20}	98.39 _{0.05}	85.96 _{0.45}	87.26 _{0.42}	85.46 _{0.21}	91.73 _{0.42}	91.69 _{0.28}	95.07 _{0.09}
Attention-MIL	79.49 _{3.20}	99.06 _{0.02}	88.50 _{0.54}	90.46 _{0.64}	85.21 _{0.74}	93.13 _{0.22}	86.20 _{3.25}	94.45 _{0.05}
DS-MIL	85.38 _{1.32}	98.65 _{0.08}	87.01 _{0.82}	90.38 _{0.67}	85.08 _{0.38}	91.69 _{0.54}	88.29 _{0.99}	94.25 _{0.07}
Transformer	87.25 _{0.59}	98.85 _{0.25}	89.02 _{0.54}	92.13 _{1.07}	87.13 _{0.71}	93.52 _{0.49}	92.12 _{0.68}	95.74 _{0.27}

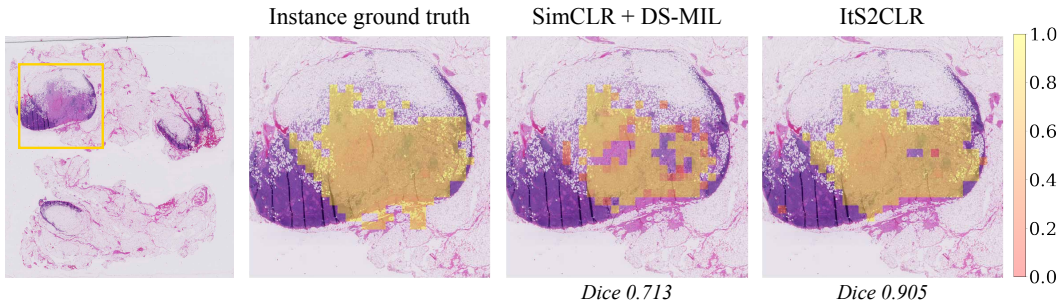


Figure 3: Tumor localization in a histopathology slide from the Camelyon16 test set. Instance-level predictions are generated by the instance-level classifier of the DS-MIL aggregator based on different instance representations. Yellow indicates higher probability of being cancerous. Transparent tiles are with probabilities less than 0.2. Appendix B.4 shows additional examples.

To perform a more exhaustive comparison of the features learned by SimCLR and ItS2CLR, we compare them in combination with several different popular MIL aggregators.¹: max pooling, top-k pooling (Shen et al., 2021b), attention-MIL pooling (Ilse et al., 2018), DS-MIL pooling (Li et al., 2021), and transformer (Chen and Krishnan, 2022) (see Appendix C for a detailed description). Table 3 shows that the ItS2CLR features outperform the SimCLR features by a large margin for all aggregators, and are substantially more stable (the standard deviation of the AUC over multiple trials is lower).

We also evaluate instance-level accuracy, which can be used to interpret the bag-level prediction (for instance, by revealing tumor locations). In Table 4, we report the instance-level AUC, F1 score, and Dice score of both ItS2CLR and the SimCLR-based baseline on Camelyon16. ItS2CLR again exhibits stronger performance. Figure 3 shows an example of instance-level predictions in the form of a tumor localization map.

4.3 COMPARISON WITH ALTERNATIVE APPROACHES

In Tables 3, 4 and 5, we compare ItS2CLR with the approaches described below. Table 6 reports additional comparisons at different *witness rates* (the fraction of positive instances in positive bags), created synthetically by modifying the ratio between negative and positive instances in Camelyon16.

Finetuning with ground-truth instance labels provides an upper bound on the performance that can be achieved through feature improvement. ItS2CLR does not reach this gold standard, but substantially closes the gap.

¹To be clear, the ItS2CLR features are learned using the DS-MIL aggregator, as described in Section 3, and then frozen before combining them with the different aggregators.

Table 4: Comparison of instance-level performance between the models in Table 3. All models use the DS-MIL aggregator. ItS2CLR achieves the best localization performance. Dice score is computed from a post-processed probability estimate described in Appendix B.2, which also includes further details and results for other aggregators.

$(\times 10^{-2})$	SimCLR (CSSL)	Ground-truth finetuning	CE finetuning		ItS2CLR			
			w/o iter.	iter.	w/o both	w/o iter.	w/o SPL	Full
AUC	94.01	97.94	95.69	96.06	95.13	95.90	96.12	96.72
F1-score	84.49	88.01	86.94	86.93	86.74	87.45	87.95	87.47
AUPRC	86.57	86.13	89.26	89.39	88.30	89.51	90.00	91.12
Dice (*)	31.79	62.17	49.11	49.41	43.74	51.70	53.03	57.86
IoU	39.53	50.24	44.98	44.88	41.37	44.56	45.41	48.27

Table 5: Comparison to models trained end-to-end, initialized with the same pretrained weights as ItS2CLR, and use the same aggregator. ItS2CLR gets better instance- and bag-level performance.

	Camelyon16 (downsampled synthetic)			Breast Ultrasound			
	Bag AUC	Instance AUC	Instance F-score	Bag AUC	Bag AUPRC	Instance AUC	Instance AUPRC
End-to-end	66.71	78.32	55.71	91.26	58.73	82.11	31.31
ItS2CLR	88.65	95.58	87.01	93.93	70.30	88.63	43.71

Cross-entropy finetuning with pseudo labels, which we refer to as *CE finetuning*, consistently underperforms ItS2CLR when combined with different aggregators, except at high witness rates. We conjecture that this is due to the sensitivity of the cross-entropy loss to incorrect pseudo labels.

Ablated versions of ItS2CLR where we do not apply iterative updates of the pseudo labels (w/o iter.), or our self-paced learning scheme (w/o SPL) or both (w/o both) achieve substantially worse performance than the full approach. This indicates that both of these ingredients are critical in learning discriminative features.

End-to-end training is often computationally infeasible in medical applications. We compare ItS2CLR to end-to-end models on a downsampled version of Camelyon16 (see Appendix A.5) and on the breast ultrasound dataset. For a fair comparison, all end-to-end models use the same CSSL-pretrained weights and aggregator as used in ItS2CLR. Table 5 shows that ItS2CLR achieves better instance- and bag-level performance than end-to-end training. The analysis in Appendix B.3 shows that end-to-end overfits quickly when the bag size is large.

4.4 IMPROVING DIFFERENT PRETRAINED REPRESENTATIONS

In this section, we show that ItS2CLR is capable of improving representations learned by different pretraining methods: supervised training on ImageNet and two non-contrastive SSL methods, BYOL (Grill et al., 2020a) and DINO (Caron et al., 2021). DINO is based on the ViT-S/16 architecture (Dosovitskiy et al., 2020), whereas the other methods are based on ResNet-18. Table 7a shows the result of initializing ItS2CLR with these features (as well as with SimCLR). The different initializations achieve varying degrees of pseudo label accuracy, but ItS2CLR improves the performance of all of them, demonstrating the robustness of the proposed framework.

5 RELATED WORK

Self-supervised learning Contrastive learning methods have become popular in unsupervised representation learning, achieving state-of-the-art self-supervised learning performance for natural images (Chen et al., 2020; He et al., 2020; Grill et al., 2020a; Caron et al., 2020; Zbontar et al., 2021; Caron et al., 2021). These methods have also shown promising results in medical imaging (Li et al., 2021; Azizi et al., 2021; Kaku et al., 2021; Zhu et al., 2022; Ciga et al., 2022). Recently, Li et al. (Li et al., 2021) applied SimCLR (Chen et al., 2020) to extract instance-level features for WSI MIL tasks and achieved state-of-the-art performance. However, Arora et al. (2019) point out the

Table 6: Bag-level AUC on Camelyon16 across different witness rates (WR): the fraction of positive instances in positive bags. All methods use the DS-MIL aggregator for a fair comparison. When the WR is low, ItS2CLR outperforms CE finetuning by a large margin. As the WR increases, CE finetuning becomes more effective.

Downsampled Instances	WR (%)	SimCLR (CSSL)	CE finetuning iterative	ItS2CLR	Finetuning w. instance GT
5% Neg.	71.2	94.52	98.55	97.58	99.11
10% Neg.	45.0	93.70	97.88	96.15	99.18
40% Neg.	23.5	90.38	93.32	95.40	97.68
Original	10.9	85.38	90.38	94.25	98.65
50% Pos.	5.8	82.47	86.96	88.52	91.81
33% Pos.	4.1	78.21	80.56	86.02	88.01

Table 7: The effects of finetuning from different initial weights on Camelyon16. (a) The bag-level prediction performance on **test** set; (b) the evaluation on instance-level prediction in **training** set.

Bag-level test AUC	ImageNet	BYOL	SimCLR	DINO (ViT)	Training ins. pred	ImageNet		BYOL		SimCLR		DINO (ViT)	
						AUC	F-score	AUC	F-score	AUC	F-score	AUC	F-score
Pretrained	0.712	0.704	0.854	0.857	Initial	0.772	0.314	0.729	0.225	0.934	0.746	0.906	0.716
ItS2CLR	0.791	0.764	0.943	0.936	Finetuned	0.835	0.598	0.804	0.288	0.973	0.783	0.972	0.806

(a)

(b)

potential issue of class collision in contrastive learning, i.e. that some negative pairs may actually have the same class. Prior works on alleviating class collision problem include reweighting the negative and positive terms with class ratio (Chuang et al., 2020), pulling closer additional similar pairs (Dwivedi et al., 2021), and avoiding pushing apart negatives that are inferred to belong to the same class based on a similarity metric (Zheng et al., 2021). In contrast, we propose a framework that leverages information from the bag-level labels to iteratively resolve the class collision problem.

There also exist non-contrastive alternatives that avoid introducing negative pairs (*e.g.* BYOL (Grill et al., 2020b), DINO (Caron et al., 2021), and SimSiam (Chen and He, 2021)). However, Wang et al. (2021) report that removing the negatives can make different object categories overlap and result in under-clustering, which limits the model’s ability to learn discriminative features.

Multiple instance learning A major part of MIL works focuses on improving the MIL aggregator. Traditionally, non-learnable pooling operators such as mean-pooling and max-pooling were commonly used in MIL (Pinheiro and Collobert, 2015; Feng and Zhou, 2017). More recent methods parameterize the aggregator using neural networks that employ attention mechanisms (Ilse et al., 2018; Li et al., 2021; Shao et al., 2021; Chen and Krishnan, 2022). This research direction is complementary to our proposed approach, which focuses on obtaining better instance representations, and can be combined with different types of aggregators (see Section 4.2).

6 CONCLUSION

In this work, we investigate how to improve feature-extraction in multiple-instance learning models. We identify a limitation of contrastive self-supervised learning: class collision hinders it from learning discriminative features in class-imbalanced MIL problems. To address this, we propose a novel framework that iteratively refines the features with pseudo labels estimated by the aggregator. Our method outperforms the existing state-of-the-art MIL methods on three medical datasets, and can be combined with different aggregators and pretrained feature extractors.

The proposed method does not outperform a cross-entropy-based baseline at very high witness rates, suggesting that it is mostly suitable for low witness rates scenarios (however, it is worth noting that this is the regime that is more commonly encountered in medical applications such as cancer diagnosis). In addition, there is a performance gap between our method and finetuning using instance-level ground truth, which suggests there is further room for improvement.

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Appendix for “Multiple Instance Learning via Iterative Self-Paced Supervised Contrastive Learning”

The appendix is organized as follows:

- In Appendix A, we include additional descriptions of the datasets (Appendix A.1), implementation details (Appendix A.2) and instructions on how to transform the Camelyon16 dataset for the additional experiments (Appendix A.5). In Appendix A.4, we provide a description of the hyperparameter selection process and report an ablation study on the Camelyon16 dataset to evaluate the sensitivity of our approach to the choice of hyperparameters.
- In Appendix B, we include additional results. In Appendix B.1, we report additional metrics to compare the pseudo label quality. In Appendix B.2, we show additional results for instance-level performance. In Appendix B.3, we report additional comparisons with end-to-end methods. In Appendix B.4, we provide additional examples of tumor localization maps.
- In Appendix C, we provide the formulation and implementation details for the different MIL aggregators used in our study.

A EXPERIMENTS

A.1 DATASET

Camelyon16 Camelyon16 is a public dataset for detection of metastasis in breast cancer. This dataset consists of 271 training and 129 test whole slide images (WSI), which are further divided into roughly 3.2 million patches at 20 \times magnification and 0.25 million patches at 5 \times magnification. On average, at 20 \times and 5 \times magnification each slide contains approximately 8,000 and 625 patches respectively. Each WSI is paired with pixel-level annotations indicating the position of tumors (if any are present). We ignore the pixel-level annotations during training and consider only slide-level labels (i.e. the slide is considered positive if it contains any annotated tumor regions). As a result, positive bags contain mixtures of patches with tumors and patches with healthy tissue. Negative bags contain only patches with healthy tissue. The ratio between positive and negative patches in this dataset is highly imbalanced. Only a small fraction of patches (less than 10%) in the positive slides contains tumor.

TCGA-LUAD TCGA for Lung Adenocarcinoma (LUAD) is a subset of TCGA (The Cancer Genome Atlas), a landmark cancer genomics program. It consists of 800 tumorous frozen whole-slide histopathology images and the corresponding genetic mutation status. Each WSI is paired with binary labels indicating whether each gene is mutated or wild type. In this experiment, we build MIL models to detect four mutations - EGFR, KRAS, STK11, and TP53, which are sensitizing mutations that can impact treatment options in LUAD (Coudray et al., 2018; Fu et al., 2020). We split the data randomly into training, validation and test sets so that each patient will appear in only one of the subsets. After splitting the data, 477 images are in the training set, 96 images are in the validation set, and 227 images are in the test set.

Breast Ultrasound dataset The Breast Ultrasound Dataset includes 28,914 ultrasound exams (Shen et al., 2021a). An exam is labeled as cancer-positive if there is a pathology-confirmed malignant finding associated with this exam. In this dataset, 5593 exams are cancer-positive. On average, each exam contains approximately 18 images. Patients in the dataset were randomly divided into a training set (60%), a validation set (10%), and test set (30%). Each patient was included in only one of the three sets. We show 5 example breast ultrasound images in Figure 4.

A.2 IMPLEMENTATION DETAILS

All experiments were conducted on NVIDIA RTX8000 GPUs and NVIDIA V100 GPUs. For all models, we perform model selection during training based on bag-level AUC evaluated on the validation set.

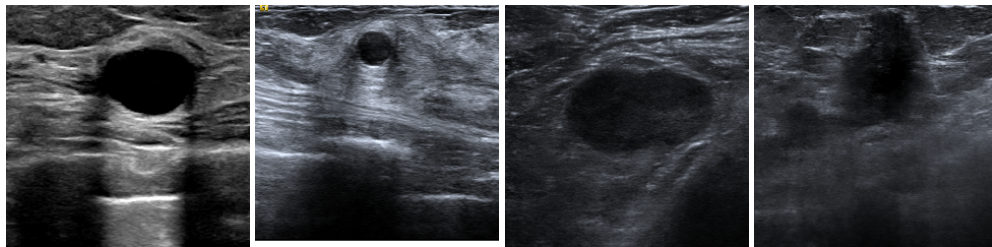


Figure 4: Example breast ultrasound images. The first two images contain a benign lesion. The second and third contain a malignant lesion. In all ultrasound images, the center object of circular shape corresponds to the lesion of interest.

Camelyon16 We follow the same preprocessing and pretraining steps as Li et. al. (Li et al., 2021). To preprocess the slides, we cropped the slides into tiles at 5x magnification, filtered out tiles that do not contain enough tissues (average saturation < 30), and resized the images into a resolution of 224 x 224 pixels. Resizing was performed using the Pillow package (Clark, 2015) with default settings (nearest neighbor sampling).

We pretrain the feature extractor, ResNet18 (He et al., 2016), with SimCLR (Chen et al., 2020) for a maximum of 600 epochs. Each patch is represented by a 512-dimensional vector. We set the batch size at 512 and temperature at 0.5. We use SGD with the learning rate of 0.03, weight decay of 0.0001, and cosine annealing scheduler. We also train a MIL aggregator using the instance features extracted by the feature extractor in order to monitor the bag AUC of the downstream task on the validation set. During finetuning with Its2CLR, we fine-tune the feature extractor for a maximum of 50 epochs.

The batch size is set to 512, and the learning rate is set to 10^{-2} . At the feature extractor training stage, we apply random data augmentation to each instance, including:

- Random ($p = 0.8$) color jittering: brightness, contrast, and saturation factors are uniformly sampled from $[0.2, 1.8]$, hue factor is uniformly sampled from $[-0.2, 0.2]$;
- Random gray scale ($p = 0.2$);
- Random Gaussian blur with kernel size of 0.06 times the size of an image;
- Random horizontal/vertical flipping with 0.5 probability.

When training the DS-MIL aggregator, we follow the settings in (Li et al., 2021). We use the Adam optimizer during training. Since each bag may contain different a number of instances, we follow (Li et al., 2021) and set the batch size to just one bag. We train each model for a maximum of 350 epochs. We use an initial learning rate of 2×10^{-4} , and use the StepLR scheduler to reduce the learning rate by 0.5 every 75 epochs. Details on the hyperparameters used for training the aggregator are in Appendix C.

TCGA-LUAD To preprocess the slides, we cropped them into tiles at 10x magnification, filtered out the background tiles that do not contain enough tissues (when average saturation is less than 30), and resized the images into the resolution of 224 x 224 pixels. Resizing was performed using the Pillow package (Clark, 2015) with nearest neighbor sampling. These tiles were color-normalized to match the Vahadane method (Vahadane et al., 2016).

To train the feature extractor, we perform the same process as for Camelyon16.

We also use DS-MIL (Li et al., 2021) as the aggregator. When training the aggregator, we resample the ratio of positive and negative bags to keep the class ratio balanced. We train the aggregator for a maximum of 100 epochs using the Adam optimizer with the learning rate set to 2×10^{-4} and reduce the learning rate by 0.5 every 50 epochs.

Breast Ultrasound We follow the same preprocessing steps as Shen et. al. (Shen et al., 2021a). All images were resized to 224 x 224 pixels using bilinear interpolation. We used ResNet18 (He et al., 2016) as the feature extractor and pretrained it using SimCLR (Chen et al., 2020) for 100 epochs. We adopt the same pretraining approach as for Camelyon16. We used the Instance Attention-MIL

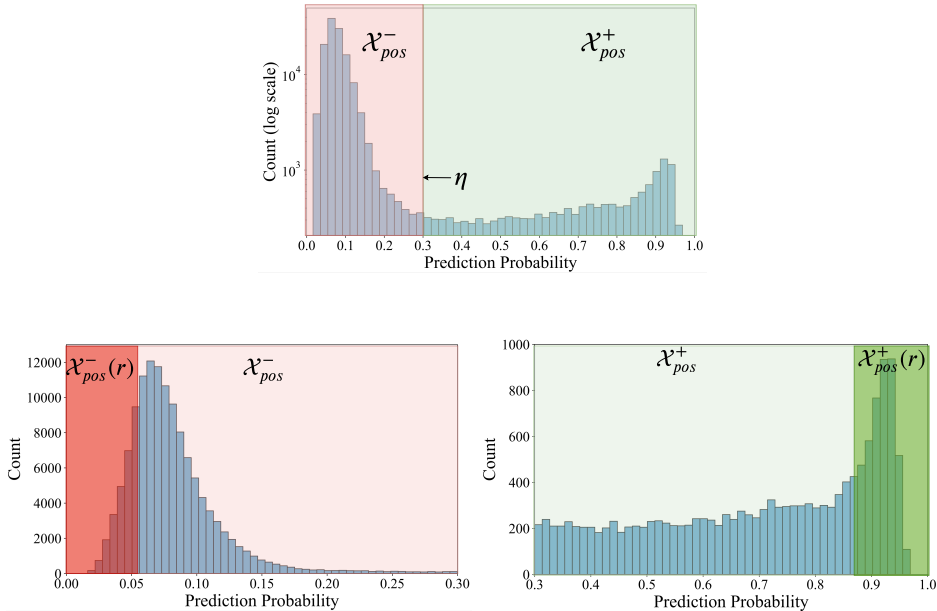


Figure 5: Illustration of our partitioning of the instances from positive bags in Section 3.2 based on the predicted probability of the instance classifier in Its2CLR. **Top:** \mathcal{X}_{pos}^+ and \mathcal{X}_{pos}^- are partitioned according to the thresholding parameter η . **Bottom:** The distribution of instance scores for instances with negative pseudo labels (left) and negative pseudo labels (right). A threshold r is symmetrically applied on both distributions so that the top $r\%$ instances with the lowest and highest scores are treated as truly negative or positive respectively. We use $\mathcal{X}_{pos}^-(r)$ and $\mathcal{X}_{pos}^+(r)$ to denote the set of instances that are deemed truly negative and positive respectively. During training, as the quality of the pseudo labels improves, we can increase r to incorporate more samples in these sets.

as an aggregator (Ilse et al., 2018). Given a bag of images x_1, \dots, x_k and a feature extractor f , the aggregator first computes instance-level predictions \hat{y}_i for each image x_i . It then calculates an attention score $\alpha_i \in [0, 1]$ for each image x_i using its feature vectors $f(x_i)$. Lastly, the bag-level prediction is computed as the average instance prediction weighted by the attention score $\hat{y} = \sum_i^k \alpha_i \hat{y}_i$. To optimize the aggregator, we trained it using Adam with a learning rate set to 10^{-3} for a maximum of 350 epochs.

A.3 COMPUTATIONAL COMPLEXITY

It takes 600 epochs (around 90 hours) to train SimCLR. Our finetuning only takes 50 extra epochs (around 10 hours), which is only 1/10 of the pretraining time. Updating pseudo labels is also efficient. Updating instance features and training MIL aggregators only take around 10 minutes, and we only do it every 5 epochs.

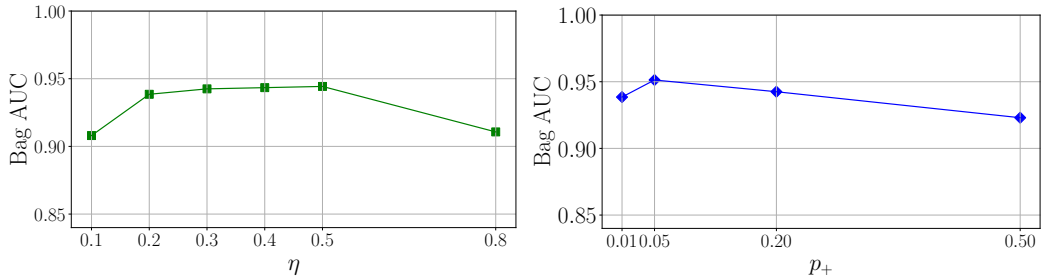
A.4 HYPERPARAMETERS OF TRAINING THE FEATURE EXTRACTOR IN ITS2CLR

Hyperparameter tuning The hyperparameters of the proposed method include: the initial threshold used for binarization of the prediction to produce pseudo labels $\eta \in [0.1, 0.9]$, the proportion of positive queries sampled $p_+ \in [0.05, 0.5]$, the initial ratio $r_0 \in [0.01, 0.7]$ and the final ratio $r_T \in [0.2, 0.8]$ of in the self-paced sampling scheme. For Camelyon16, we obtain the highest bag-level validation AUC using the following hyperparameters: $\eta = 0.3$, $p_+ = 0.2$, $r_0 = 0.2$ and $r_T = 0.8$. We use the feature extractor trained under this setting in Tables 2, 3 and 4. The complete list of hyperparameters in different experiments is reported in Table 8.

Sensitivity analysis We conduct the sensitivity analysis for each hyperparameter on Camelyon 16, and observe a robust performance over a range of hyperparameter values.

Table 8: Its2CLR hyperparameters used in our experiments.

	Camelyon16	Breast Ultrasound	TCGA-LUAD mutation			
			EGFR	KRAS	STK11	TP53
η	0.3	0.3	0.3	0.5	0.3	0.5
r_0	0.2	0.2	0.2	0.2	0.2	0.2
r_T	0.8	0.8	0.8	0.8	0.8	0.8
p_+	0.2	0.2	0.5	0.2	0.2	0.2

Figure 6: Sensitivity analysis for the threshold η and the ratio of positive pseudo labels used as query images p_+ on the Camelyon16 dataset.

- *Threshold η* : The choice of η influences the instance-level pseudo labels. As shown in Figure 5, the outputs of the instance-level classifier are mostly close to 0 or 1, so the pseudo labels do not dramatically vary for a wide range of η . We conducted a small ablation experiment on the importance of η . Figure 6 (left) shows that Its2CLR is quite robust to the value of η , except for some extreme values. If η is too small (e.g. 0.1), it can introduce a significant number of false positives. If η is too large (e.g. 0.8), it can mistakenly exclude some useful positive samples, causing a drop in the performance. In the main paper, since negative instances are more prevalent than positive instances, a threshold of 0.3 (less than 0.5) can increase the recall for the positive instances.
- *Sampling ratio of query instance over pseudo labels*: We use p_+ to denote the percentage of positive query instances used during the contrastive learning stage. Figure 6 (right) shows that it is desirable to choose a relatively small p_+ . Since there are far fewer positive instances than negative instance, keeping the ratio of positive queries low can avoid repetitively sampling from a limited number of positive instances. Also, since the negative instance set $\mathcal{X}_{\text{neg}}^-$ is clean, there is more label noise among the positive pseudo labels.
- *The initial rate r_0 and final rate r_T for the self-paced sampling scheduler*: Figure 7 shows that Its2CLR is also generally robust to the r_0 and r_T . However, extremely large initial rate r_0 (high confidence in the pseudo labels) may introduce more noise during the training and hurt the performance. Conversely, extremely small r_T (low confidence in the pseudo labels) may prohibit the model from using more data, also hurting performance.
- *Sampling during warm-up*: During the warmup phase, we sample query instances from $\mathcal{X}_{\text{neg}}^-$. An alternative choice can be sampling we sample the query instance from $\mathcal{X}_{\text{pos}}^+$ and the corresponding set \mathcal{D}_x from $\mathcal{X}_{\text{neg}}^-$. However, our experiments show that the resulting bag-level AUC drops to 90.91% under this setting, which is significantly lower than 94.25% by the proposed method. This comparison demonstrates the importance of using clean negative instances as query images during warmup.

A.5 EXPERIMENTS ON SYNTHETIC VERSIONS OF CAMELYON16

Simulation of witness rates (WR)

Since the ground truth instance-level labels are available for Camelyon16, we can conduct experiments on synthetic versions of the dataset to study the impact of the prevalence of positive instances

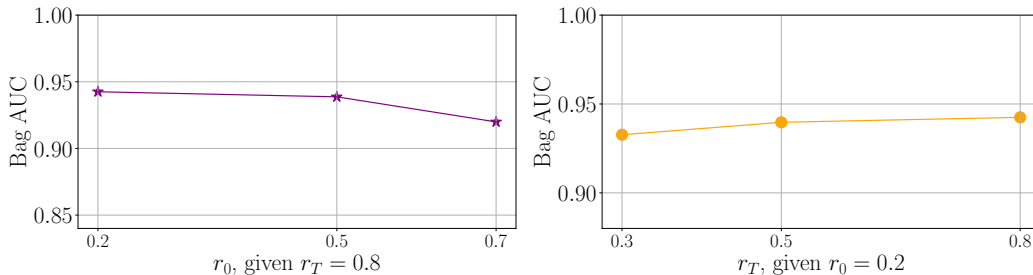


Figure 7: Sensitivity analysis for the hyperparameters r_0 and r_T of the proposed self-paced learning scheme on Camelyon16.

on the performance of the proposed approach and the baselines. Section 2 describes how the performance of CSSL is affected by low *witness rates* (fraction of positive instances in each positive bag). To study the robustness of the proposed framework to the witness rate in the data, we increase or decrease the witness rate of Camelyon16 by randomly dropping negative or positive instances within each bag respectively. The percentage of retained instances and the resulting witness rates are reported in Table 6.

Downsampled version of Camelyon16 for end-to-end training

In order to enable end-to-end training we downsample each bag in Camelyon16 to around 500 instances so that it fits in the memory of a GPU. To achieve this, we divide the large bag into smaller bags while keeping the witness rate of each sub-bag at a similar level as the original bag. In more detail, if the bag size is smaller or equal to 500, we keep the original bag. If the bag size is greater than 500, we divide the bag into several sub-bags such that each sub-bag contains approximately 500 instances. After that, we randomly divide the negative instances within the original bag into desired number of sub-bags evenly. For the positive bag, we randomly partition the positive instances within the original bag into desired number of sub-bags evenly as well. If the number of positive instances within that positive bag is smaller than the desired number of sub-bags, we correct the number of sub-bags to be the number of positive instances. We then combine the positive instances and the negative instances to form sub-bags. This ensures that the bag-level label is correct and the witness rate for each positive sub-bag remains similar to the original bag.

A.6 DESCRIPTION OF THE ABLATION STUDY

Details for CE finetuning with/without Iterative Updating

- *CE + w/o iterative updating*: we use the same set of the initial pseudo labels as our Its2CLR framework. All the instances within the negative bags are labeled as negative, for instances in positive bags, we assign the pseudo label according to the instance prediction by the aggregator. In the following finetuning epochs of the aggregator, the pseudo label is kept fixed.
- *CE + iterative updating*: based on CE + w/o iterative updating, the pseudo label is updated every few epochs, which is in turn used to guide the finetuning. We will make sure that this is explained clearly in the revised version of the paper.

Details for Its2CLR With/ without SPL.

- *Its2CLR without iterative update*: We keep everything the same as the full Its2CLR procedure (including the SPL strategy), but we do not apply steps 7, 8 and 9 in Algorithm 1. As a result, the pseudo labels are fixed to always equal the initial set of pseudo labels.
- *Its2CLR without SPL*: We keep everything the same as the full Its2CLR procedure (including iterative updating), but modify step 10 in Algorithm 1. We do not utilize the pseudo label to train the model in a self-paced learning way as in Section 3.2. We utilize all the pseudo-labeled data from the beginning of the finetuning.

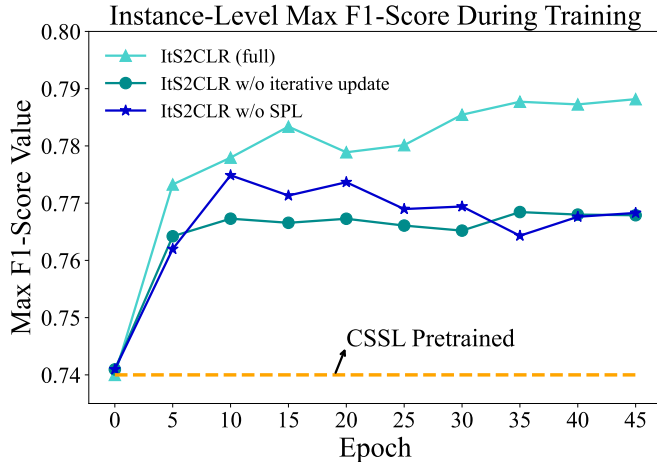


Figure 8: Max F1 score comparison. ItS2CLR updates the features iteratively based on a subset of the pseudo labels that is selected according to the self-paced learning (SPL) strategy. On Camelyon16, this gradually improves the accuracy of the pseudo labels in terms of instance-level max F1 score. Both the iterative updates and SPL are important to achieve this.

B ADDITIONAL RESULTS

We present here additional results to supplement those presented in Section 4.

B.1 LEARNING CURVES

F1-Score plot corresponding to Figure 1: In Figure 8, we show the max F1 score curve corresponding to the right side of Figure 1. This plot confirms the importance of self-paced learning and iterative updating in ItS2CLR.

Instance pseudo label AUC comparison with cross-entropy finetuning: Figure 9 compares ItS2CLR with an alternative approach that finetunes the feature extractor using cross-entropy (CE) loss on the Camelyon16 dataset. Without iterative updating, CE finetuning rapidly overfits to the noise in the pseudo labels. Iterative updating prevents this to some extent, but does not match the performance of ItS2CLR, which produces increasingly accurate pseudo labels as the iterations proceed.

B.2 INSTANCE-LEVEL EVALUATION

In order to evaluate instance-level performance, we report classification metrics including AUC, F1-score, AUPRC and Dice score for localization.

The Dice score is defined as follows:

$$\text{Dice} = \frac{2 \sum_i y_i p_i}{\sum_i y_i + \sum_i p_i}, \quad (4)$$

where y_i and p_i are the ground truth and predicted probability for the i th sample. It penalizes the prediction with low confidence. The predicted probability is computed from the output of the MIL model s_i via linear scaling:

$$p_i = \sigma(as_i + b), \quad (5)$$

where $a \in [-5, 5]$ and $b \in [0.1, 10]$ are chosen to maximize the Dice score on the validation set.

Max pooling aggregator: In Table 4, we show that our model achieves better weakly supervised localization performance compared to other methods when DS-MIL is used as the aggregator. In Table 9, we show that the same conclusion holds for an aggregator based on max-pooling.

Linear evaluation: In Table 10, we report results obtained by training a logistic regression model using the features obtained from the same approaches in Table 4, following a standard linear eval-

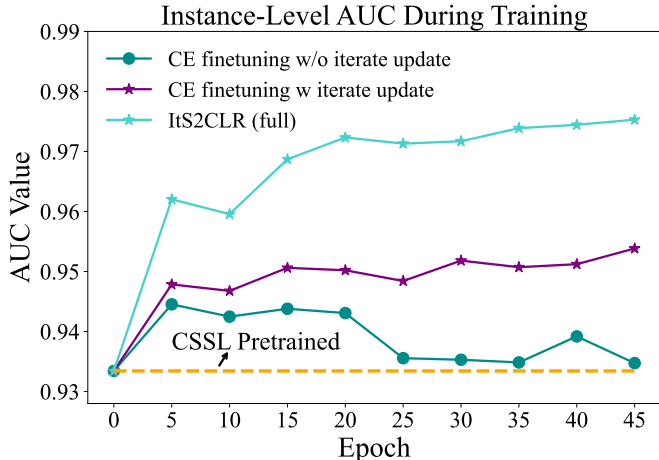


Figure 9: Comparison of instance-level pseudo label quality between ItS2CLR and an alternative approach that finetunes the feature extractor using cross-entropy (CE) loss on the Camelyon16 dataset. Iterative updating improves performance for CE finetuning, but ItS2CLR produces more accurate pseudo labels.

Table 9: Comparison of instance-level performance for the models in Table 3, using a max pooling aggregator.

$(\times 10^{-2})$	SimCLR (CSSL)	Ground-truth finetuning	CE finetuning		ItS2CLR			
			w/o iter.	iter.	w/o both	w/o iter.	w/o SPL	Full
AUC	91.53	97.58	93.17	94.48	92.69	94.55	94.43	96.25
F1-score	78.45	88.24	85.26	85.83	86.77	86.05	87.52	86.75
AUPRC	79.94	85.50	85.79	86.73	85.50	84.54	86.80	89.99
Dice	31.21	63.01	43.90	44.76	46.57	55.30	52.55	57.82

uation pipeline in representation learning (Chen et al., 2020). ItS2CLR again achieves the best instance-level performance. We also produce bag-level predictions using the maximum output of the linear classifier for each bag, which again showcases that instance-level performance results in superior bag-level classification.

B.3 COMPARISON WITH END-TO-END TRAINING

In this section we provide additional results to complement Table 5, where ItS2CLR is compared to end-to-end models. The end-to-end training is conducted with the same aggregators for each dataset as described in Section 4 and Appendix A.2.

Camelyon16 Figure 10 shows that an end-to-end model trained on the downsampled version of Camelyon16 described in Section A.5 rapidly overfits when trained from scratch and from SimCLR-pretrained weights. The two-stage model, on the other hand, is less prone to overfitting. Table 11 shows that the two-stage learning pipeline outperforms end-to-end training, and is in turn outperformed by ItS2CLR.

Breast Ultrasound dataset Table 12 shows that for the breast-ultrasound dataset end-to-end training outperforms the SimCLR+Aggregator baseline, but is outperformed by ItS2CLR.

B.4 TUMOR LOCALIZATION MAPS

Figure 11 provides additional tumor localization maps.

Table 10: Comparison of instance-level performance for the models in Table 3, using a linear classifier trained on the frozen features produced by each model. In addition, we produce bag-level predictions using the maximum output of the linear classifier for each bag.

($\times 10^{-2}$)	SimCLR	Ground-truth	CE finetuning		Its2CLR			
Instance-level	(CSSL)	finetuning	w/o iter.	iter.	w/o both	w/o iter.	w/o SPL	Full
AUC	96.13	97.56	96.94	96.88	96.64	97.25	96.92	97.27
F1-score	85.29	87.69	87.34	86.94	86.00	87.07	87.6	87.92
AUPRC	82.65	85.94	79.96	78.02	78.17	84.56	77.90	82.09
Dice	49.56	61.39	55.40	54.66	51.85	54.87	55.11	60.13
Bag-level (max-pooling)								
AUC	86.25	97.37	87.53	90.54	89.97	93.09	92.81	97.47

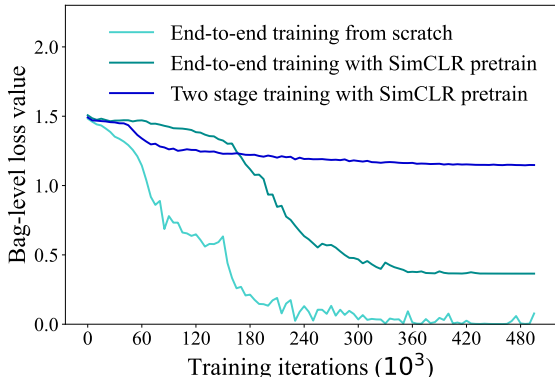


Figure 10: Comparison between end-to-end training and two-stage training on the downsampled version of the Camelyon16 dataset. End-to-end models overfit rapidly. Note that the unit of the training iterations here is 1k.

C MIL AGGREGATORS

C.1 FORMULATION OF MIL AGGREGATORS

In this section, we describe the different MIL aggregators benchmarked in Section 4.2 and Table 3.

Let \mathcal{B} denote a collection of sets of feature vectors in \mathbb{R}^d . The bags of extracted features in the dataset are denoted by $\{H_b\}_{b=1}^B \subset \mathcal{B}$. An aggregator is defined as a function $g : \mathcal{B} \rightarrow [0, 1]$ mapping bags of extracted features to a score in $[0, 1]$.

There exist two main approaches in MIL:

1. *The instance-level approach*: using a logistic classifier on each instance, then aggregating instance predictions over a bag (e.g. max-pooling, top k-pooling).
2. *The embedding-level approach*: aggregating the instance embeddings, then obtaining a bag-level prediction via a bag-level classifier (e.g. attention-based aggregator, Transformer).

We denote the embeddings of the instances within a bag by $H = \{h_k\}_{k=1}^K$, where K is the number of instances.

Max-pooling obtains bag-level predictions by taking the maximum of the instance-level predictions produced by a logistic instance classifier ϕ , that is

Table 11: Results on the downsampled version of the Camelyon16 dataset.

	End-to-end (scratch)	End-to-end (SimCLR)	SimCLR + DS-MIL	ItS2CLR
Bag AUC	64.52	66.71	80.96	88.65
Instance AUC	78.32	81.29	93.94	95.58
Instance F-score	51.02	55.71	85.93	87.01

Table 12: Results on the Breast Ultrasound dataset.

	SimCLR + Aggregator	End-to-end MIL	ItS2CLR
Bag AUC	80.79	91.26	93.93
Bag AUPRC	34.63	58.73	70.30
Instance AUC	62.83	82.11	88.63
Instance AUPRC	10.58	31.31	43.71

$$g_\phi(H) = \max_{k=1, \dots, K} \{\phi(h_k)\}. \quad (6)$$

Top-k pooling Shen et al. (2021b) produces bag-level predictions using the mean of the top- M ranked instance-level predictions produced by a logistic instance classifier ϕ , where M is a hyperparameter.

Let $\text{top}M(\phi, H)$ denote the indices of the elements in H for which ϕ produces the highest M scores,

$$g_\phi(H) = \frac{1}{M} \sum_{k \in \text{top}M(\phi, H)} \phi(h_k). \quad (7)$$

Attention-based MIL Ilse et al. (2018) aggregates instance embeddings using a sum weighted by attention weights. Then the bag-level estimation is computed from the aggregated embeddings by a logistic bag-level classifier φ :

$$g_\varphi(H) = \varphi \left(\sum_{k=1}^K a_k h_k \right), \quad (8)$$

where a_k is the attention weight on instance k . a_k is computed by:

$$a_k = \frac{\exp(w^T \tanh(Vh_k^T))}{\sum_{j=1}^K \exp(w^T \tanh(Vh_j^T))}, \quad (9)$$

where $w \in \mathbb{R}^{p \times 1}$ and $V \in \mathbb{R}^{p \times d}$ are learnable parameters and p is the dimension of the hidden layer.

DS-MIL combines instance-level and embedding-level aggregation, we refer to DS-MIL (Li et al., 2021) for more details on this approach.

Transformer Chen and Krishnan (2022) aggregation uses an L -layer Transformer to process the set of instance features H . The initial set $H^{(0)}$ is set equal to H . Then it goes through Transformer as following:

$$\begin{aligned} H^{(l)} &= \text{MSA} \left(H^{(l-1)} \right) + H^{(l-1)} \\ H^{(l)} &= \text{MLP} \left(H^{(l-1)} \right) + H^{(l-1)} \end{aligned} \quad (10)$$

for $l = 1, \dots, L$, where MSA is multiple-head self-attention, MLP is a multi-layer perceptron network. Then the processed vectors $H^{(l)}$ are fed to **Attention-based MIL** (Ilse et al., 2018) to obtain bag-level predictions.

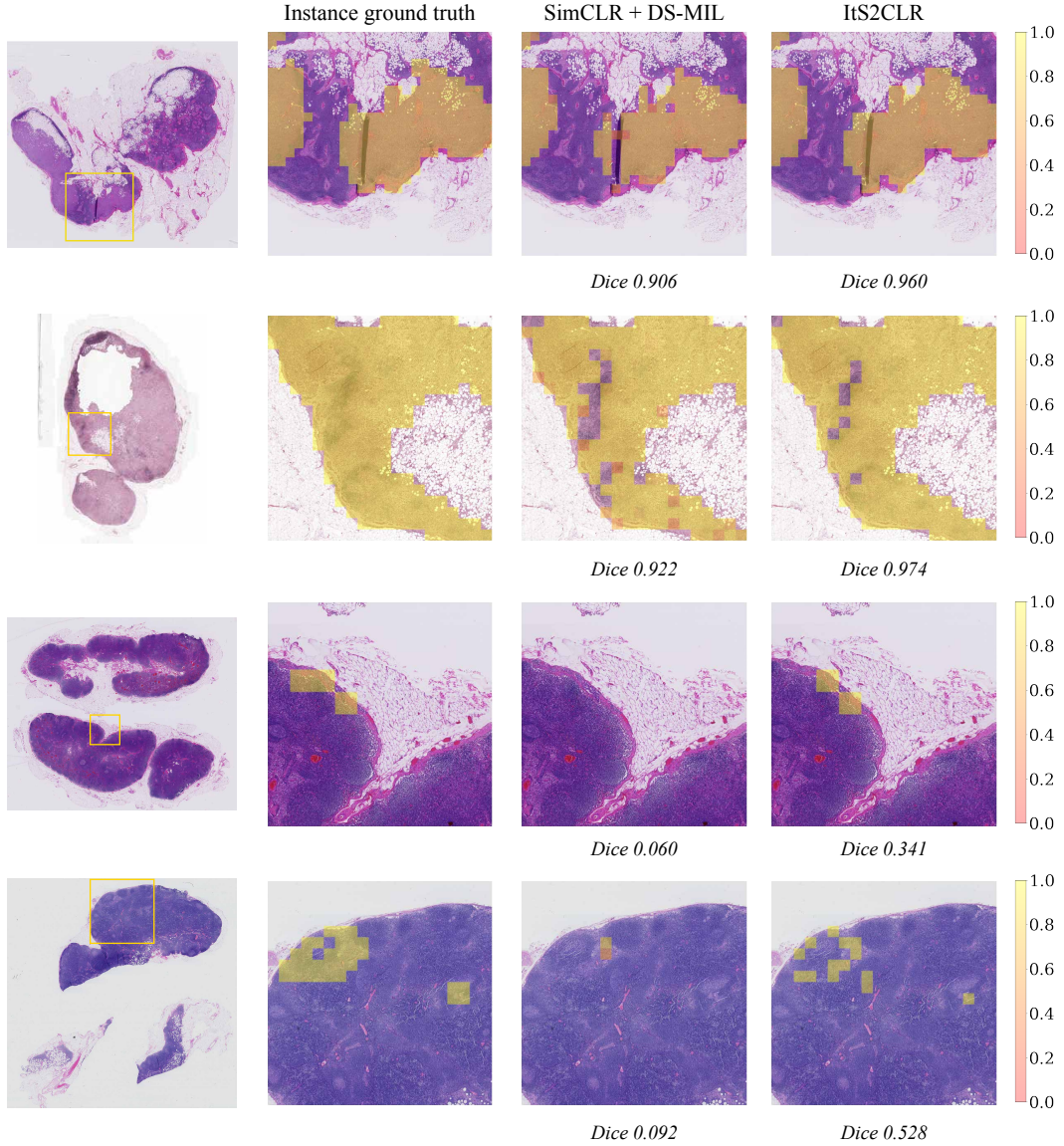


Figure 11: Additional tumor localization maps for histopathology slides from the Camelyon16 test set. Instance predictions are generated by the instance classifier of the DS-MIL trained on extracted instance-level features.

$$g_{\varphi}(H^l) = \varphi \left(\sum_{k=1}^K a_k h_k^l \right), \quad (11)$$

where a_k is the attention weight on instance k . a_k is computed by:

$$a_k = \frac{\exp(w^T \tanh(V(h_k^l)^T))}{\sum_{j=1}^K \exp(w^T \tanh(V(h_j^l)^T))}, \quad (12)$$

where $w \in \mathbb{R}^{p \times 1}$ and $V \in \mathbb{R}^{p \times d}$ are learnable parameters and p is the dimension of the hidden layer.

C.2 IMPLEMENTATION DETAILS

Top-k pooling we select the ratio in Top-k pooling from the set $\{0.1\%, 1\%, 3\%, 10\%, 20\%\}$.

DS-MIL The weight between the two cross-entropy loss functions in DS-MIL is selected from the interval $[0.1, 5]$ based on the best validation performance.

Attention-based MIL. The hidden dimension of the attention module to compute the attention weight is set equal to the dimension of the input feature vector (512).

Transformer. We add a light-weighted two-layer Transformer blocks to process instance features. We did not observe increase in performance with additional blocks.