Deep Weakly-Supervised Learning Methods for Classification and Localization in Histology Images: A Comparative Study

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\textbf{ABSTRACT}

Using deep learning models to diagnose cancer from histology data presents several challenges, including image size, stain variation, and labels ambiguity. In addition, cancer grading and localization of regions of interest (ROIs) in these images normally relies on both image- and pixel-level labels, the latter requiring a costly annotation process. Deep weakly-supervised object localization (WSOL) methods provide different strategies for low-cost training of deep learning models. Using only image-class annotations, these methods can be trained to classify an image, and yield class activation maps (CAMs) for ROI localization. First, this paper provides a review of state-of-art DL methods for WSOL. We propose a taxonomy where these methods are divided into bottom-up and top-down methods according to the information flow in models. Although the latter have seen limited progress, recent bottom-up methods are currently driving much progress with deep WSOL methods. Early works focused on designing different spatial pooling functions. However, these methods reached limited localization accuracy, and unveiled a major limitation – the under-activation of CAMs which leads to high false negative localization. Subsequent works aimed to alleviate this issue and recover complete object, using different techniques such as perturbation, self-attention, shallow features, pseudo-annotation, and task decoupling. Then, representative deep WSOL methods from our taxonomy are evaluated and compared in terms of classification and localization accuracy on two challenging histology datasets – one for colon cancer (GlaS), and a second for breast cancer (CAMELYON16). Overall, the results indicate poor localization performance, particularly for generic methods that were initially designed to process natural images. Methods designed to address the challenges of histology data often use priors such as ROI size, or additional pixel-wise supervision estimated from a pretrained classifier, allowing them to achieve better results. However, all methods suffer from high false positive/negative localization. Classification performance is mainly affected by the model selection process, using either the classification or localization metric. Finally, four key challenges are identified for the application of deep WSOL methods in histology – under/over activation of CAMs, sensitivity to thresholding, and model selection – and research avenues are provided to mitigate these issues. Our code is publicly available\textsuperscript{1}.

\textbf{Keywords:} Medical/Histology Image Analysis, Computer-Aided Diagnosis, Deep Learning, Weakly Supervised Object Localization, Weakly Supervised Learning, Image Classification

1 Introduction

The advent of Whole Slide Imaging (WSI) scanners has opened new possibilities in pathology image analysis (He et al., 2012; Madabhushi, 2009). Histology slides provide more comprehensive views of diseases and their effect on tissue (Hipp et al., 2011) since their preparation preserves the underlying tissue structure (He et al., 2012). For instance, some disease characteristics (e.g. lymphatic infiltration of cancer) may be predicted using only histology images (Gurcan et al., 2009). The analysis of histology images remains the gold standard in diagnosing several diseases, including most types of cancer (Gurcan et al., 2009; He et al., 2012; Veta et al., 2014). Breast cancer which is the most prevalent cancer in women worldwide, leverages medical imaging systems as a primary diagnosis tool for its early detection (Daisuke and Shumpei, 2018; Veta et al., 2014; Xie et al., 2019).

Cancer is mainly diagnosed by pathologists who analyze WSIs to identify and assess epithelial cells organized into ducts, lobules, or malignant clusters, and embedded within a heterogeneous stroma. Manual analysis of histology tissues depends heavily on the expertise and experience of histopathologists. Such manual interpretation is time consuming and difficult to grade in a reproducible manner. Analyzing WSIs from digitized histology slides enables facilitated, and potentially automated, Computer-Aided Diagnosis in pathology, where the main goal is to confirm the presence or absence of disease and to grade or measure disease progression.

Given the large number of digitized exams, automated systems have become a part of the clinical routines for breast cancer detection (Tang et al., 2009). Automated analysis of the spatial structures in histology images could be traced back to early

\textsuperscript{1}Code: https://github.com/jeromerony/survey_wsl_histology
works (Bartels et al., 1992; Hamilton et al., 1994; Weind et al., 1998). Different techniques for image processing and machine learning (ML) have been investigated for identifying discriminative structures and classifying histology images (He et al., 2012), including thresholding (Gurcan et al., 2006; Petushi et al., 2006), active contours (Bamford and Lovell, 2001), Bayesian classifiers (Naik et al., 2007), graphs to model spatial structures (Bilgin et al., 2007; Tabesh et al., 2007), and ensemble methods based on Support Vector Machines and Adaboost (Doyle et al., 2006; Qureshi et al., 2008). An overview of these techniques and their applications is provided in (Gurcan et al., 2009; He et al., 2012; Veta et al., 2014).

Recently, deep learning (DL) models have attracted much attention in histology image analysis (Belharbi et al., 2021; 2022a; 2022b; Courtiol et al., 2018; Dimitriou et al., 2019; Iizuka et al., 2020; Janowczyk and Madabhushi, 2016; Li and Ping, 2018; Srinidhi et al., 2019). In this paper, we focus on the application of DL models in histology image analysis.

DL models (Goodfellow et al., 2016), and in particular convolutional neural networks (CNNs), provide state-of-the-art performance in many visual recognition applications such as image classification (Krizhevsky et al., 2012), object detection (Redmon et al., 2016), and segmentation (Dolz et al., 2018). These supervised learning architectures are trained end-to-end with large amounts of annotated data. More recently, the potential of DL models has begun to be explored in assisted pathology diagnosis (Daisuke and Shumpei, 2018; Janowczyk and Madabhushi, 2016; Li and Ping, 2018). Given the growing availability of histology slides, DL models have not only been proposed for disease prediction (Hou et al., 2016; Li and Ping, 2018; Sheikhzadeh et al., 2016; Spanhol et al., 2016a; Xu et al., 2016), but also for related tasks like detection and segmentation of tumor regions within WSI (Kieffer et al., 2017; Mungle et al., 2017), scoring of immunostaining (Sheikhzadeh et al., 2016; Wang et al., 2015), cancer staging (Shah et al., 2017; Spanhol et al., 2016a), mitosis detection (Chen et al., 2016; Cireşan et al., 2013; Roux et al., 2013), gland segmentation (Caie et al., 2014; Gertych et al., 2015; Sirinukunwattana et al., 2017), and detection and quantification of vascular invasion (Caicedo et al., 2011).

Histology images present additional challenges for ML/DL models because of their (1) high resolution where, for instance, a single core of prostate biopsy tissue digitized at 40× magnification is approximately \((15000 \times 15000)\) elements \((\sim 225\) million pixels); (2) heterogeneous nature resulting mainly from variation of the WSI production process; and (3) noisy/ambiguous labels (Daisuke and Shumpei, 2018) caused by the annotation process that is conducted by assigning the worst stage of cancer to the image. Therefore, a WSI that is annotated with a specific grade is more likely also to contain regions with lower grades. This leads to imbalanced datasets having fewer images with high grades. Noisy/ambiguous labels are an issue for models trained through multi-instance learning (Carbonneau et al., 2018; Cheplygina et al., 2019; Wang et al., 2018; Zhou, 2004), where the WSI label is transferred to sampled image patches, and can introduce annotation errors. Such label inconsistency can degrade model performance, and entangle learning (Frenay and Verleysen, 2014; Sukhbaatar et al., 2014; Zhang et al., 2017) (see Figs. 1 and 2).

Training accurate DL models to analyze histology images often requires full supervision to address key tasks, such as classification, localization, and segmentation (Daisuke and Shumpei, 2018; Janowczyk and Madabhushi, 2016). Learning to accurately localize cancerous regions typically requires a large number of images with pixel-wise annotations. Considering the size and complexity of such images, dense annotations come at a considerable cost, and require highly trained experts. Outsourcing this task to standard workers such as Mechanical Turk Worker is not an option. As a result, histology datasets are often comprised of large images that are coarsely-annotated according to the diagnosis. It is therefore clear that training powerful DL models to simultaneously predict the image class, while localizing important image regions linked to a prediction without dense annotations is highly desirable for histology image analysis.

Despite its intrinsic challenges (Choe et al., 2020), techniques for weakly-supervised learning (WSL) (Zhou, 2017) have recently emerged to alleviate the need for dense annotation, in particular for computer vision applications. These techniques are adapted to different forms of weak supervision including image-tags (image-level label) (Kim et al., 2017; Pathak et al., 2015; Teh et al., 2016; Wei et al., 2017), scribbles (Lin et al., 2016; Tang et al., 2018), points (Bearman et al., 2016), bounding boxes (Dai et al., 2015; Khoreva et al., 2017), global image statistics, such as target size (Bateson et al., 2019; Jia et al., 2017; Kervadec et al., 2019a;b). The reduced requirement

Figure 1: Segmentation of two WSIs from the ICIAR 2018 BACH Challenge. Colors represent different types of cancerous regions: red for Benign, green for In Situ Carcinoma and blue for Invasive Carcinoma. These examples highlight the diversity in size and regions (Aresta et al., 2018).
of weak supervision provides an appealing learning framework. In this paper, we focus on WSL methods that allow to train a DL model using only image-level annotations for classification of histology images and for localization of image ROI linked to class predictions. These methods perform the weakly-supervised object localization (WSOL) task, which can produce localization under the form of activation maps and bounding boxes (Choe et al., 2020).

Interpretability frameworks (Samek et al., 2019; Zhang et al., 2021) have attracted much attention in computer vision (Alber et al., 2019; Bau et al., 2017; Belharbi et al., 2021; Dabkowski and Gal, 2017; Feng et al., 2019; Feng and Vedaldi, 2017; Goh et al., 2020; Murdoch et al., 2019; Petsiuk et al., 2018; 2020; Ribeiro et al., 2016; Samek et al., 2020; Zhang et al., 2020b), and medical image analysis (Cruz-Roa et al., 2013; De La Torre et al., 2020; Fan et al., 2020; Ghosal and Shah, 2020; Hägele et al., 2020; Hao et al., 2019; Korbar et al., 2017; Saleem et al., 2021; Tavolaro et al., 2020). It is related to WSOL in the sense that it also allows to provide a spatial map associated with a class prediction decision. However, interpretability methods are often evaluated differently, using for instance the pointing game (Zhang et al., 2018b), which is a loose way to localize an object via a point. Therefore, we limit the focus of this paper to DL models in the literature that were designed and evaluated mainly for the localization task.

Currently, Class Activation Mapping (CAM) methods represents the most common technique for WSOL (Belharbi et al., 2022c). Strong spatial activation in CAMs correspond to ROI (Zhou et al., 2016). In addition to providing ROI localization, CAMs can be considered as a visual interpretation tool (Samek et al., 2019) to localized image regions linked to the model’s prediction of a cancer type, which is a highly desirable property in decision support systems. These ROI can be further inspected by a pathologist or followed by other automatic procedures.

In this work, we provide a review of state-of-art deep WSOL methods proposed between the year of 2013 and early 2022. Most of the reviewed methods have been proposed and evaluated on natural image datasets. Only few of them have been developed and evaluated with histology images in mind. The performance of representative methods undergo a comparison over two public histology datasets for breast and colon cancer to assess their performance in term of classification and localization performance. While there has been different reviews of ML/DL models for medical image analysis, and in particular for analysis of histology WSIs (Daisuke and Shumpei, 2018; Janowczyk and Madabhushi, 2016; Kandemir and Hamprecht, 2015; Litjens et al., 2017; Sudharshan et al., 2019) and medical video analysis (Quellec et al., 2017), they have focused on fully supervised, semi-supervised, or a mixture of different learning settings for classification and segmentation tasks (Litjens et al., 2017; Srinidhi et al., 2019). To our knowledge, this paper presents the first review focused on deep WSOL models, trained on data with image-class labels for classification of histology images, and localization of ROIs.

The deep WSOL methods in the literature are divided into two main categories based on the flow of information in models: bottom-up and top-down methods. Our review showed that research in top-down methods are more active and dominant compared to top-down methods making them state-of-the-art techniques. To address the shortcomings of CAMs, bottom-up methods have progressed from designing simple spatial pooling techniques, to performing perturbations and self-attention, to using shallow features, and most recently to exploiting pseudo-annotation and separating the training of classification from localization tasks. Recent successful WSOL techniques combine the usage of shallow features, with pseudo-annotation while decoupling classification and localization tasks. In top-down techniques, there is less progress. These methods usually rely either on biologically-inspired processes, gradient, or confidence scores to build CAMs. The results of our comparative study showed that deep WSOL methods proposed for histology data can yield good results, yet generic methods initially proposed for natural images produced poor results. The former methods often rely on priors that aim to reduce false positives/negatives such as the ROI size, or use explicit pixel-wise guidance collected from pre-trained classifiers. Overall, all WSOL methods suffer from high false positive/negative localization. We discussed several issues of applying such methods on histology data, including: under/over-activation of CAMs, sensitivity to thresholding, and model selection. Over-activation of CAMs is a new behavior that caused potentially by the visual similarity between foreground and background.

In section 2, a taxonomy and review of state-of-the-art deep WSOL methods is provided, followed by our experimental methodology (section 3) and results (section 4). We conclude this work with a discussion of the main findings, key challenges of applying such WSOL methods in histology, and provide future directions to mitigate these challenges, and potentially reduce the gap in performance between WSOL.
and fully supervised methods. More experimental details are provided in Appendix A and Appendix B. In addition, more visual results of localizations are presented in Appendix C. Our code is publicly available.

2 A taxonomy of weakly-supervised object localization methods

In our taxonomy, we focus on deep WSL methods that allow to classify an image and pixel-wise localize its ROIs via a

heat map (soft-segmentation map, CAM)\(^2\) During training, only global image-class labels are required for supervision. These methods are referred to as weakly-supervised object localization methods (WSOL) (Choe et al., 2020).

Figure 3 illustrates the overall taxonomy. Among deep WSL methods, we identify two main categories based on the information flow in the network to yield region localization (see Figure 4): (a) bottom-up methods that are based on the forward pass information within a network, and (b) top-down methods that exploit the backward information in addition to forward pass. Each WSL aims to stimulate the localization of ROI using a different mechanism. Both categories rely on building a spatial attention map that has high magnitude response over ROI and low activations over background. The rest of this section provides the notation to ease presenting different methods, details on the main categories and sub-categories, and highlights of the main emerging trends that contributed in the progress of WSL task.

Figure 3: An overall taxonomy of deep WSL methods for training on data with global image-class annotations, and classification and ROI localization. Methods in each category are ordered chronologically. 1. **Bottom-up**: relies on the forward pass information. 2. **Top-down**: Exploits both forward and backward pass information.

Figure 4: An illustration of the main difference between bottom-up (top) and top-down (bottom) methods for deep WSL. Both approaches produce CAMs. However, bottom-up techniques produce them during the forward pass, while top-down techniques require a forward, then a backward pass to obtain them. The numbers 1, 2, 3 in circles indicate the order of operations. The top-down methods can either produce CAMs at the top before the class pooling or the input of the network.
**Notation.** To describe the mechanisms behind different methods, we introduce the following notation. Let us consider a set of training samples \( D = \{ (x^{(i)}, y^{(i)}) \} \) of images \( x^{(i)} \in \mathbb{R}^{D \times H_i \times W_i} \) with \( H_i, W_i \) and \( D \) being the height, width and depth of the input image respectively; and its image-level label (i.e. class) is \( y^{(i)} \in \mathcal{Y} \) with \( C \) possible classes. For simplicity, we refer to a training sample (an input and its label) as \( (x, y) \).

Let \( f_\theta : \mathbb{R}^{D \times H_i \times W_i} \rightarrow \mathcal{Y} \) be a function that models a neural network where the input \( x \) has an arbitrary height and width and \( \theta \) is the set of model parameters. The training procedure aims to optimize parameters \( \theta \) to achieve a specific task. In a multi-class scenario, the network typically outputs a vector of scores \( s \in \mathbb{R}^C \) in response to an input image. This vector is then normalized to obtain a posterior probability using a softmax function,

\[
\Pr(y = i | x) = \text{softmax}(s)_i = \frac{\exp(s_i)}{\sum_{j=1}^C \exp(s_j)}.
\]

The model predicts the class label corresponding to the maximum probability: \( \text{argmax}\{\Pr(y = i | x) : i = 1, 2, ..., C\} = \text{argmax}\{s_i : i = 1, 2, ..., C\} \).

Beside the classification of the input image, we are also interested in the pixel-wise localization of ROI within the image. Typically, a WSOL method can predict a set of \( C \) activation maps of height \( H \) and width \( W \) to indicate the location of the regions of each class. We note this set as a tensor of shape \( M \in \mathbb{R}^{C \times H \times W} \); where \( M_c \) indicates the \( c \)-th map. \( M \) is commonly referred to as Class Activation Maps (CAM). Due to convolutional and downsampling operations, typical CAMs have low resolution compared to the input image. We note the downscale factor as \( S \) called such that \( H = H_i / S \) and \( W = W_i / S \). Interpolation is often required to yield a CAM with same size as the image.

### 2.1 Bottom-up WSOL techniques

In bottom-up methods, the pixel-wise localization is based on the activation of the feature maps resulting from the standard flow of information within a network from the input layer into the output layer (forward pass, Figure 4 (top)). Within this category, we identify two different subcategories of techniques to address weakly supervised localization. The first category contains techniques that rely mainly on spatial pooling. Different ways were proposed to pool class scores while simultaneously stimulating spatial response in CAM to localize ROI. These methods had limited success. Therefore, another type of methods emerges that aims directly to refine CAMs while using simple spatial pooling techniques. In the next subsections, we present these methods and their variants.

### 2.2 Spatial pooling methods

This family of techniques aim to design different spatial pooling techniques to compute per-class scores which are then used to train the whole network for classification using standard cross-entropy. In some cases, the pooling is performed to build an image representation, i.e. bag features. Such spatial pooling allows to build maps (CAMs) to localize ROI. Each method promotes differently the emergence of the localization of ROI. Such strategy is at the core of WSOL and it is considered a pioneering mechanism that introduced weakly supervised localization in deep models (Lin et al., 2013). By preserving spatial information in CAMs, learning this way allows localization of ROI to emerge while requiring only global class annotation. Different methods have been proposed to compute the class-scores from spatial maps where each pooling strategy has a direct impact on the merging localization. The challenge is to stimulate only ROI to emerge in the CAM. The beginning of the pipeline is usually the same for all techniques – a CNN extracts \( K \) feature maps \( F \in \mathbb{R}^{K \times H \times W} \), where \( K \) is the number of feature maps which is architecture-dependent. The feature maps \( F \) are then used to compute a per-class score using a spatial pooling technique.

The first work is Global Average Pooling (GAP) method (Lin et al., 2013). It simply averages each feature map in \( F \in \mathbb{R}^{K \times H \times W} \) to yield the per-map score in order to build the global representation \( f \in \mathbb{R}^K \) of the input image,

\[
f_k = \frac{1}{HW} \sum_{i=1,j=1}^{H,W} F_{k,i,j},
\]

where \( f_k \) is the \( k \)-th feature of the output. The class-specific activations are then obtained by a linear combination of the features using the weights of the classification layer. Note that in practice, one can directly average CAMs, when available, to yield per-class scores instead of using an intermediate dense layer. In both cases, this pooling strategy ties the per-class score to all spatial locations in a map. This means that both ROI and background participate in the buildup of the per-class score. Authors in CAM method (Zhou et al., 2016) show that this pooling strategy can be used to obtain a localization ability in a CNN using only global labels. Typically, in a CNN, the last layer which classifies the representation \( f \) is a fully connected layer parametrized by \( W \in \mathbb{R}^{C \times K} \) such that \( s = W f \) (bias is omitted for simplicity). The CAMs, denoted as \( M \in \mathbb{R}^{C \times H \times W} \), are then obtained using a weighted sum of the spatial feature \( F \),

\[
M_c = \sum_{k=1}^K W_{c,k} F_k.
\]

This strategy has been widely used for natural scene images as well as for medical images (Feng et al., 2017; Gondal et al., 2017; Izadyyazdanabadi et al., 2018; Sedai et al., 2018).
The early work of CAM (Zhou et al., 2016) showed a fundamental issue which is under-activation. CAMs tend to activate only on small discriminative regions therefore localizing only small part of the object while missing large part of it. This leads to high false negatives. Subsequent works in WSOL aim mainly to tackle this issue by pushing activations in CAM to cover entire object. This is performed either through a different pooling strategy or explicitly designing a method that aims to uncover full object (subsubsection 2.2.1).

As an alternative to averaging spatial responses, authors in (Oquab et al., 2015) consider using the maximum response value on the CAM as a per-class score (MAX-Pool). Therefore, this method avoids including potential background regions into the class score therefore reducing false positives. However, this pooling technique tends also to focus on small discriminative parts of objects since the per-class score is tied only to one pixel of the response map. To alleviate this problem, authors in (Pinheiro and Collobert, 2015; Sun et al., 2016) consider using a smoothed approximation of the maximum function to discover larger parts of objects of interest using log-sum-exp function (LSE),

\[ s_c = \frac{1}{q} \log \left[ \frac{1}{H \times W} \sum_{i=1,j=1}^{H,W} \exp(q \cdot M_{c,i,j}) \right], \tag{4} \]

where \( q \in \mathbb{R}^+ \) controls the smoothness of the approximation. A small value of \( q \) makes the approximation closer to the average function while a large \( q \) makes it close to the maximum function. Thus, small values of \( q \) make the network consider large regions while large values consider only small regions.

Instead of considering the maximum of the map (Oquab et al., 2015), i.e. a single high response point, authors in (Zhou et al., 2018) (PRM) propose to use local maxima. This amounts in using local peak responses which is more likely to cover large part of the object compared to using only the single maximum response,

\[ s_c = M^c \ast G^c = \frac{1}{N^c} \sum_{k=1}^{N^c} M^c_{k,i,j}, \tag{5} \]

where \( G^c \in \mathbb{R}^{H \times W} \) is a sampling kernel, \( \ast \) is the convolution operation, and \( N^c \) is the number of local maxima. Depending on the size of the kernel, this pooling allows stimulating different distant locations which can help recover adjacent regions with an object. In the same way, it is likely that background regions are stimulated. This highlights the challenge of transferring global label into local pixels. Note that such transfer of supervision is known to be ill-posed in WSOL field (Wan et al., 2018).

All the pooling methods discussed so far rely on high responses to yield per-class score. The assumption over CAMs is that strong responses indicate potential ROI, while low responses are more likely to be a background. Such assumption is incorporated in computing per-class scores, and therefore, has a direct impact on the localization in CAMs. Authors in (Durand et al., 2017; 2016) (WILDCAT) pursue a different strategy by including low activation, i.e. negative evidence, in the computation of the per-class score. They argue that such pooling plays a regularization role and prevents overfitting allowing better classification performance. However, it remains unclear how tying negative regions to class scores improve localization since the aim is to maximize the per-class score of the true label. However, authors provide architectural change of the pooling layer where several modality maps per-class are considered. Hence, these modalities allow capturing several parts of the object leading to a better localization. Formally, the pooling is written as,

\[ s_c = \frac{Z^+_c}{n^+} + \alpha \frac{Z^-_c}{n^-}, \tag{6} \]

where \( Z^+_c \) and \( Z^-_c \) correspond to the sum of the \( n^+ \) highest and \( n^- \) lowest activations of \( M_c \), respectively and \( \alpha \) is a hyper-parameter that controls the importance of the minimum scoring regions. Such an operation consists in selecting for each class the \( n^+ \) highest activation and the \( n^- \) lowest activation within the corresponding map. This method has also been used in the medical field for weakly supervised region localization and image classification in histology images (Belharbi et al., 2019; 2022b). In (Courtiol et al., 2018), instead of operating on pixels, authors consider adapting (Durand et al., 2017; 2016) for WSIs to operate on instances (tiles).

The aforementioned methods build a bag (image) representation, then compute CAMs that holds local localization responses, then finally pull the per-class scores. Authors in (Ilse et al., 2018) (Deep MIL) rely explicitly on multi-instance learning (MIL) framework (Carbonneau et al., 2018; Cheplygina et al., 2019; Wang et al., 2018; Zhou, 2004). First, instance representations are built. Then, using attention mechanism (Bahdanau et al., 2015), a bag representation is computed using a weighted average of the instances representations. In this case, it is the attention weights that represent the CAM. Strong weights indicate instances with ROI, while small weights indicate background instances. This method requires changes to standard CNN models. In addition, it is tied to binary classification only. Adjusting to multi-class requires furthermore changes to the architecture. Formally, given a set of features \( F \in \mathbb{R}^{K \times H \times W} \) extracted for an image,
the representation $f$ of the image is computed as,

$$f = \sum_{i=1,j=1}^{H,W} A_{i,j} F_{i,j},$$

and

$$A_{i,j} = \frac{\exp(\psi(F_{i,j}))}{\sum_{i=1,j=1}^{H,W} \exp(\psi(F_{i,j}))},$$

Where $F_{i,j}$ is (by an abuse of notation) the feature vector of the location ($i.e.$ instance) indexed by $i$ and $j$. $\psi: \mathbb{R}^K \rightarrow \mathbb{R}$ is a scoring function. The resulting representation $f$ is then classified by a fully connected layer. Two scoring functions are considered (Ilse et al., 2018),

$$\psi_1(f) = \mathbf{w} \tanh(\mathbf{V} f),$$

$$\psi_2(f) = \mathbf{w} \left[ \tanh(\mathbf{V} f) \odot \sigma(\mathbf{U} f) \right],$$

where $\mathbf{w} \in \mathbb{R}^L$, $(\mathbf{V}, \mathbf{U}) \in \mathbb{R}^{L \times K}$ are learnable weights, and $\odot$ is element-wise multiplication. This approach is designed specifically for binary classification and produces a matrix of attention weights $A \in [0,1]^{H \times W}$ with $\sum A = 1$. In the next section, we present a second bottom-up category that aims directly to refine the CAMs.

### 2.2.1 CAM refinement methods

While spatial pooling methods have helped the emergence of some discriminative regions in CAMs, they have limited success to cover full object. Under-activation of CAMs is still a major ongoing issue in WSOL field which reflects the difficulty to transfer global label into pixel-level. Since this became clear, research directions have been shifted from improving the pooling function to explicitly overcome under-activation issue and recover the entire object. Often, this is achieved while using simple pooling function such as GAP method (Lin et al., 2013). Different strategies have been proposed to do so. We divide them into two main categories: methods that use data augmentation to mine more discriminative regions, and methods that aim to enhance and learn better internal features of a CNN.

#### Data augmentation methods

Data augmentation is strategy often used in machine learning to prevent overfitting and improve performance (Goodfellow et al., 2016). In the same way, it has been used in WSOL field to prevent models from overfitting one single discriminative region, i.e. under-activate. Often, this is achieved by pushing the model to seek, i.e. mine, other discriminative regions, thereby promoting large coverage of objects in CAM. The most common data augmentation is information suppression, i.e. erasing, where part of an input signal is deleted. This can be performed over input images or intermediate features. Conceptually, this can be seen as a perturbation process to stimulate more ROI to emerge. For instance, authors in (Singh and Lee, 2017) propose a 'Hide-And-Seek' (HaS) training strategy where the input image is divided into multiple patches. During training phase, only some of these patches are randomly set to be visible while the rest are hidden. Such data augmentation has already been shown to regularize CNN models and improve their classification performance (Devries and Taylor, 2017) (cutout). This is similar to applying dropout (Srivastava et al., 2014) over input image where the target regions are a whole patch instead of a single pixel. As a result, the network will not rely on the most discriminative patches too much and will seek other discriminative regions. While this is an advantage, it can be counter-productive as the network may be pushed unintentionally to consider background as discriminative especially for small objects that can be easily deleted.

Other data augmentations were exploited to improve localization. For instance, MixUp method (Zhang et al., 2018a) was designed to regularize neural networks by making them less sensitive to adversarial examples, and reduce their memorization. This is done by blending two training images to some degree where the label of the augmented image is assigned by the linear combination of the labels of the two images. Despite the augmented images look unnatural and locally ambiguous, it improves classification accuracy. Authors in (Yun et al., 2019) (CutMix) have adapted this method to improve localization. Instead of fully blending images, they propose to randomly cut a patch from an image and mix it with a second image. The label is proportionally mixed to the size of the patch. In essence, this is similar to cutout (Devries and Taylor, 2017) and HaS (Singh and Lee, 2017) but instead of filling patches with black or random noise, it is filled with pixels from another image. In practice, this has been shown to improve localization performance. However, due to the randomness in the source patch selection process, this method may select background regions leading to wrong mixed labels which itself leads the classifier to learn unexpected feature representations. Similarly, (Kim et al., 2020) proposed PuzzleMix which jointly optimizes two objectives: selecting an optimal mask and an optimal mixing plan. The mixing of the input images is no longer random but use image saliency that emerges from image statistics. The mask tries to reveal most salient data of two images. Meanwhile, the optimal transport plan aims to maximize the saliency of the revealed portion of the data. In the same direction, SaliencyMix (Uddin et al., 2021) exploits image saliency but uses bounding box to capture region remix instead of a mask. Note that relying on image saliency is a major drawback for less salient images such as histology data since foreground and background look similar. Authors in (Stegmüller et al., 2022) (ScoreMix) applied this type of approach on histology data by using proposed regions via attention. Mixing region is based on classifier attention instead of image statistics. Discriminative regions from the sources are cut and mixed over non-discriminative regions of the target. Conceptually, this gives a better regional mixing. However, since the learned
attention can easily hold false positives/negative, the mixing can still be vulnerable. In addition, the obtained results seem relatively close to CutMix method (Yun et al., 2019).

In (Wei et al., 2017) (AE), authors propose an iterative strategy to mine discriminative regions for semantic segmentation. Similar to HaS method (Singh and Lee, 2017), they erase regions with the highest response values through learning epochs of a classifier. This allows large parts of the model to emerge. The emerging segmentation proposals are used to train the model for semantic segmentation. The sequential erasing yields a computationally expensive process since multiple rounds are required. To improve this, ACoL (Zhang et al., 2018c) designs two branch classifiers to predict the discriminative region and corresponding complementary area at the same time. MEIL method (Mai et al., 2020) goes in the same direction by adding multiple output branches that exploits erasing integrated learning.

Guided Attention Inference Network methods (GAIN) (Li et al., 2018) uses two sequential networks with a shared backbone to mine ROI. The first network yields an attention map of ROI which is used to erase discriminative regions in the image. Erased image is then fed to the next network where its class response with respect to the target label is used to make sure no discriminative regions are left in the image after the erasing process. The suppression process of ROI is expected to push the first model to seek more discriminative regions, hence large ROI are covered by the CAM. Similarly, authors in (Kam et al., 2017) (Two-Phase) consider two-phase training of two networks. The first network is trained until convergence. Then, it is used, with frozen weights, in front of a second network to produce CAM of the target label. The CAM is thresholded to localize most discriminative regions. Instead of masking the input image as in GAIN method (Li et al., 2018), authors consider masking intermediate feature maps. Results show again that this type of information hiding at feature level allows exploring more discriminative regions, hence large ROI are covered by the CAM. Similarly, authors in (Belharbi et al., 2019) (RecMin) consider a recursive mining algorithm integrated directly into the back-propagation allowing mining ROI on the fly. All these methods perform mining-erasure of information over the input image. ADL (Choe and Shim, 2019) method builds a self-attention map per layer to spot potential ROI. Then, stochastically erases locations over multiple intermediate feature maps at once during forward-propagation through simple element-wise multiplication. The erasing is performed by simple dropout over the attention mask. Such a procedure allows to enhance both classification and localization performance. Note that self-attention has already been used prior to ADL in (Zhu et al., 2017) (SPN) as a layer to yield proposal regions which are coupled with feature maps allowing only potential ROI to pass to the next layer filtering out background/noise. Authors in (Belharbi et al., 2022b) (MAXMIN) use two models: a localizer, followed by a classifier. The localizer aims to build a CAM to localize ROI at pixel-level. The input image is masked by the produced CAM, then fed to the classifier. The authors explicitly include the background prior into learning the CAM by constraining it to hold both foreground and background regions. This prevents under/over activations which in turn reduces false positives/negatives. Using entropy, the target classifier scores are constrained to be low over background and high over foreground to ensure that there is no ROI left in the background. An important downside of these erasing/mining-based methods is the risk of over-mining since there is no clear criteria to stop mining. While being efficient to expand and gather object regions, it is very easy to expand to non-discriminative regions which directly increases false positives.

Features enhancement methods. Other methods aim to improve localization by learning better features. This is often achieved through architectural changes of standard models or by exploiting different level of features for localization such as shallow features. Additionally, using pseudo-labels to explicitly guide learning has emerged as a different approach to tackle WSOL task.

Authors in (Wei et al., 2018) analyze the impact of object scale on predictions and propose to exploit dilated-convolution (Chen et al., 2018; 2015). They equip a classifier with a varying dilation rates: multi-dilated convolutional (MDC) blocks. This has shown to effectively enlarge the receptive fields of convolutional kernels and more importantly transfer the surrounding discriminative information to non-discriminative object regions, promoting the emergence of ROI while suppressing background. Unlike most works that pull CAM from the top layer (high level), authors in (Yang et al., 2020) (NL-CCAM) consider non-local features by combining low and high level features to promote better localization. In addition, rather than using a per-class map as final CAM, they combine all CAMs using a weighted sum after ordering them using their posterior class probabilities. This allows gathering several parts of the objects and suppress background regions in the final localization map. FickleNet method (Lee et al., 2019) randomly selects hidden locations
over feature maps. During training, for each random selection, a new CAM is generated. Therefore, for each input image, multiple CAMs can be generated to predict the most discriminative parts. This allows building CAMs that better cover the object. This work is related to ADL (Choe and Shim, 2019) which uses attention followed by dropout to mask features. FickleNet does not rely on attention, and simply drops random locations.

DANet (Xue et al., 2019) uses multi-branches output at different layers to yield a CAM with different resolution. This allows to obtain a hierarchical localization. To spread activation over entire object without deteriorating classification performance, the authors consider a joint optimization of two different terms. A discrepant divergent activation loss constrains the CAMs of the same class to cover different regions. The authors note that classes with similar visual features are typically suppressed in standard CNNs since they are not discriminative. To recover these regions, authors propose a hierarchical divergent activation loss. In a hierarchical manner, meta-classes are created to gather previous meta-classes where the bottom of the hierarchy contains the original classes. At a specific level, the classifier is trained to assign the same meta-class for all samples assigned to it. This pushes shared similar features to activate within that meta-class, hence recovering similar features in original classes.

In I²C method (Zhang et al., 2020c), the authors propose to leverage pixel-wise similarities at spatial feature level via Inter-Image Communication (I²C) for better localization. Local and global discriminative features are pushed to be consistent. A local constraint aims to learn the stochastic feature consistency among discriminative pixels that are randomly sampled from a pair of images within a batch. A global constraint is employed where a global center feature per-class is maintained and updated in memory after each minibatch. Average local random features are constrained to be close to the center class features. ICL method (Ki et al., 2020) aims to deal with over-activation by preventing CAMs from spiking over background. An attention contrastive loss is proposed. Similar to ADL (Choe and Shim, 2019), an attention map is estimated from feature maps. Very high and very low activations are used to estimate potential foreground and background regions. The middle activations could be either foreground or background. To expand the activation from foreground into that uncertain region, the contrastive loss aims to push activation with spatial features similar to foreground features to be foreground while activations with similar spatial features to background features are pushed to be background. This allows a careful expanding of foreground activation toward background regions. In addition, attention at the top layer, which is semantically rich, is used in a self-learning setup to align and guide low layer attention which is often noisy.

WSOL task has benefited also from recent advances in architectural design in deep learning. Transformers (Dosovitskiy et al., 2021) in particular has seen their first use in such task in the method TS-CAM (Gao et al., 2021). Visual transformer (Dosovitskiy et al., 2021) constructs a sequence of tokens by splitting an input image into patches with positional embedding and applying cascaded transformer blocks to extract visual representation. Visual transformers can learn complex spatial transforms and reflect long-range semantic correlations adaptively via self-attention mechanism and multilayer perceptrons. This happens to be crucial for localizing full object extent. TS-CAM (Gao et al., 2021) improves patch embeddings by exploiting self-attention. In addition, a class-agnostic map is built at each layer. Authors equipped transformers output with a CAMs module allowing obtaining semantic maps. Final CAM is an aggregation between the CAM yielded by the CAMs module and the average class-agnostic maps across all layers. This shows to help improve localization. In CSTN method (Meethal et al., 2020), the authors replace standard convolution filters with Spatial Transformer Networks (STNs) (Jaderberg et al., 2015). In addition to using multi-scale localization, this STN model learns affine transformations that can cover different variations including translation, scale, and rotation, allowing to better attend different object variations.

Recently, a new trend has emerged in WSOL in which pseudo-annotations are exploited. An external model or a WSOL classifier is initially trained using weak labels. Then, it is used to collect pseudo-labels which are a substitution to the missing full supervision. They are then used to finetune a final model. This provides explicit localization guidance for training. However, such methods inherit a major drawback which is learning with inaccurate/noisy labels which must be dealt with. For instance, in (Rahimi et al., 2020) (PairSim), the authors use a fully supervised source dataset to train a proposal generator (Faster-RCNN (Ren et al., 2015)). Then, they apply the generator over a target weakly supervised dataset for WSOL task to yield proposals per sample, i.e. bag. Classical MIL framework (Carbonneau et al., 2018; Cheplygina et al., 2019; Wang et al., 2018; Zhou, 2004) is applied by splitting target dataset into 2 subsets conditioned on the class; one with positive samples with that class label, and the other holds negative samples. MIL framework is solved in way to yield exactly one proposal per positive sample. A unary score about the proposal abjectness that is learned from the source is used, in addition to a pairwise score that measures the compatibility of two proposals conditioned on the bag class.

Authors in (Zhang et al., 2020a) show that localization and classification interfere with each other in WSOL, and that these should be divided into two separate tasks. They first train a classifier which is used to generate Pseudo Supervised
Object Localization (PSOL). Such pseudo-supervision is then used to train a separate class-agnostic localization. In the same direction, the work in (Wei et al., 2021) demonstrates the benefits of shallow features for localization. The authors exploit low level (Shallow) features to yield Pseudo supervised Object Localization (SPOL) which are used to guide training another network. F-CAM method (Belharbi et al., 2022c) exploits as well shallow features by equipping standard classifiers with a segmentation decoder to form a U-Net architecture (Ronneberger et al., 2015). Such model builds the final CAM through top and low features using skip-connections. The authors show the impact of CAM size on localization performance where the smaller the CAM size the lower the localization performance. CAMs are often interpolated to yield same size as input image. Since interpolation algorithm does not take in consideration the image statistics, they propose to gradually increase the resolution of the CAMs via a parametric decoder. Low resolution CAM, image statistics, and generic size priors, are used to train the decoder. The authors propose a stochastic sampling of local evidence as opposite to common practices in literature where pseudo-labels are selected and fixed before training. Following F-CAM architecture, NEGEV (Belharbi et al., 2022a) is proposed for histology dataset to improve localization and classifier interpretability. However, the authors focus mainly on using negative evidence collected from pre-trained classifier, as well as naturally occurring in dataset set, i.e. fully negative samples. This allows this method to achieve state-of-the-art performance in localization. Additional experiments show as well that the stochastic sampling proposed in (Belharbi et al., 2022c) outperforms, with a large margin, fixed selection of local evidence. Self-Produced Guidance method (SPG) (Zhang et al., 2018d) extracts several attention maps from top and low level layers to benefit from global and detailed localization. Discrete location of potential ROI are collected from the maps using thresholding which are then used to train different layers in a self-supervised way. Note that this approach is related to SPN (Zhu et al., 2017) and ADL (Choe and Shim, 2019) that exploit attention as a self-guidance mechanism to steer the focus toward potential ROI by masking feature maps. However, SPG method explicitly learns a segmentation mask using discrete pixel-wise information collected from attention as supervision.

2.3 Top-down WSOL techniques

This second main category is based essentially on the backward pass information within a network to build an attention map that localizes ROI with respect to a selected target class (backward pass, Figure 4 (bottom)). We distinguish three main sub-categories that differ in the way the top signal is backtraced. The first category exploits a secondary conductive feedback network. The second category relies on gradient information to aggregate backbone spatial feature maps while the last category exploits posterior class scores for the aggregation.

**Biologically-inspired methods.** These methods are often inspired by cognitive science. For instance, authors in (Cao et al., 2015) argue that visual attention in humans is typically dominated by a target, i.e., ‘goal’, in a top-down fashion. Biased competition theory (Beck and Kastner, 2009; Desimone, 1998; Desimone and Duncan, 1995) explains that human visual cortex is enhanced by top-down stimuli and irrelevant neurons are suppressed in feedback loops when searching for objects. The work in (Cao et al., 2015) mimics this top-down loop with a feedback network that is attached to standard feedforward networks and holds binary variables in addition to ReLU activations (Nair and Hinton, 2010). These binary variables are activated by top-down message. Given a target class, a standard forward step is performed within the feedforward network to maximize the posterior score of the target. Then, a backward pass is achieved within the feedback network. To promote selectivity in the feedback loop (Desimone and Duncan, 1995), $L_1$ norm is used as a sparsity term over the binary variables of the feedback network. The process of forward/backward is performed several times in order to optimize a loss function composed of the posterior score of a target class, and the sparsity term over the binary variables. For localization task, the backward loop can reach the network input layer to yield an attention map that indicates ROI associated with the target class selected at the top of the network. Despite the benefits of this method for CNN visualization and ROI localization, its iterative optimization process to obtain localization makes it less practical for WSOL task. Excitation-backprop (Zhang et al., 2018b) method follows a similar top-down scheme. In particular, the authors consider a top-down Winner-Take-ALL (WTA) process (Tsotsos et al., 1995) which select one winning path. To avoid selecting one deterministic path, which is less representative and lead to binary maps, authors propose a probabilistic WTA downstream process that models all paths. This process integrates both bottom-up and top-down information to compute winning probability for each neuron. To improve the localization accuracy of the attention map, in particular for images with multi-objects, authors propose a contrastive top-down attention which captures the differential effect between a pair of top-down attention signals. This allows the attention map to hold activations only for one target class. While both methods (Cao et al., 2015; Zhang et al., 2018b) yield good results, they require substantial changes to standard CNN architectures. In addition, these methods are often used for interpretability and explainability of deep models (Samek et al., 2019).

We describe in the next two categories how intermediate spatial feature maps are used to pull discriminative maps to lo-
calize ROI associated with a fixed target class. Usually, an aggregation scheme via a weight per feature map is performed. The key element in these methods is how the weighting coefficients are estimated. All these weights are back-streamed from the per-class posterior score at the top of the network.

**Grad-based aggregation.** This family of methods relies on the gradient of posterior class scores of the true label with respect to the feature maps to determine aggregation weights. Such approaches are also used as visual tools to explain a network’s decision (Samek et al., 2019). In (Selvaraju et al., 2017), the authors propose Grad-CAM method. In order to compute the CAMs, they propose to aggregate spatial feature maps using gradient coefficients. The coefficient of each feature map is computed using the gradient of the score of the selected target class with respect to that map. Such gradient indicates how much a pixel-location contributes to the target output. The CAM for the class \( c \) is computed as,

\[
M_c = \text{relu} \left( \sum_{k=1}^{K} A_{c,k} F_k \right),
\]

where \( A_{c,k} = \frac{1}{H \times W} \sum_{i=1}^{H} \sum_{j=1}^{W} \frac{\partial s_c}{\partial F_{k,i,j}} \),

where \( s_c \) is the score for class \( c \). This approach is a generalization of the CAM method (Zhou et al., 2016) where the derivative of the score with respect to the feature map is used instead of learned weights. This approach has been improved in Grad-CAM++ (Chattopadhyay et al., 2018) and Smooth-Grad-CAM++ (Omeiza et al., 2019) to obtain better localization by covering a complete object, as well as explaining occurrence of multiple instances in a single image. In (Fu et al., 2020), the authors propose theoretical grounds for CAM-based methods in particular Grad-CAM for more accurate visualization. They include two important axioms: sensitivity and conservation which determine how to better compute the importance weight of each feature map. Following these axioms, the authors propose a new gradient-based method, XGrad-CAM, which computes the coefficient differently. The coefficients are the solution to an optimization problem composed of the two axioms. So far, these methods aggregate the feature maps at the last layer. LayerCAM method (Jiang et al., 2021) exploits top and low level layers to extract localization. Top layers are commonly known to hold coarse localization, while low level layers hold detailed but noisy localization. This method extracts CAM from each layer using back-propagated gradient signal. Then, the final CAM is computed by fusing all CAMs estimated at each layer. Note that this family of methods are designed to interrogate a pre-trained model. While they are model-independent allowing inspecting the decision of a trained model, the user lacks a way to control their behavior during the training of the model. This makes the localization performance of these methods strongly tied to the localization information provided by the trained model.

**Confidence-based aggregation.** Several methods exploit raw scores of the target class, instead of gradient, in order to aggregate spatial features of a backbone. In Score-CAM method (Wang et al., 2020), each feature map is element-wise multiplied with the input image, then it is used to compute the target-class score. This allows one to obtain a posterior score for each spatial map which is then compared to the score of raw image. The difference between both scores yields Channel-wise Increase of Confidence (CIC) where high values indicate that presence of strong ROI in the feature map. The final CAM is a linear weighted sum of all the feature maps, followed by ReLU non-linearity (Nair and Hinton, 2010) where CIC coefficients are used as weights,

\[
M_{\text{Score-CAM}}^c = \text{ReLU} \left( \sum_k \alpha_k^c F_k \right),
\]

where \( \alpha_k^c \) is the CIC of class \( c \) for feature map \( k \); \( l \) is a layer. Smoothed-Score-CAM (SS-CAM) (Naidu and Michael, 2020) improves Score-CAM (Wang et al., 2020). Instead of computing the CIC over a single masked image, SS-CAM averages many perturbed masked images. The authors propose either to perturbate the feature map or the input image. This yields smoothed aggregation weights. IS-CAM method (Naidu et al., 2020) performs similar process to smooth weights. While these methods yield good localization, recent empirical evaluation showed that they are computational expensive (Belharbi et al., 2022c). For instance, computing a single CAM for an image of size 224 × 224 over ResNet50 (He et al., 2016) model takes few minutes on a descent GPU. This makes training such methods impractical. In Ablation-CAM method (Desai and Ramaswamy, 2020), the authors consider a gradient-free method to avoid using gradients due to its unreliability due to gradient saturation (Adebayo et al., 2018; Kindermans et al., 2019). The importance coefficient of a feature map is computed as slope that measures the difference between posterior class score and the score obtained when turning off that feature map. That different is then normalized.

### 2.4 Critical Analysis

Our review of several works in WSOL field between the year 2013 to the beginning of 2022 showed the emergence of different strategies for WSOL task. We cite two main families. Top-down methods that aim to back trace posterior probability class to find ROI. These methods rely either on biology processes, classifier confidence, or gradients. Gradient based methods are most dominant. They are model-independent and can be used to any trained network; in addition of being easy to implement. This family of methods is also used for CNN visualization, and interpretability (Samek et al., 2019).
While top-down methods have been successful, they have seen slow progress compared to bottom-up methods which seem to be the driving core of WSOL. Most successful WSOL methods are from this family. They are easy to implement and follow standard flow of information in feed-forward networks. Early works aimed to design different spatial pooling functions to obtain CAMs. These methods quickly hit a fundamental issue in CAMs that is under-activation. This suggests also that relying only on spatial pooling to transfer global labels into pixel-level is not enough. Subsequent works focus mainly on this issue by aiming to recover localization of complete object. Several strategies have been proposed:

- **perturbation** of input images or embeddings, i.e. intermediate features. It is often used to mine discriminative regions. The common perturbation mechanism is suppression where part of the signal is deleted stochastically either uniformly or via selective attention.

- **self-attention and self-learning.** Training CNNs to localize objects using only global labels is an ill-posed problem (Wan et al., 2018). However, thanks to convolution filter properties, common patterns can emerge within intermediate spatial feature maps. Researchers exploit this property to collect self-attention maps which often focuses on objects. Such self-attention has been successfully used to guide intermediate convolution layers to focus further more on emerging ROI and filter out background and noisy features. In addition, most certain regions in a self-attention map have been used as a self-supervisory signal at pixel-level.

- **shallow features** have been known for long time to hold useful but noisy localization information in supervised learning such as in segmentation (Ronneberger et al., 2015). It is until recently that shallow features are exploited as well in WSOL task allowing to boost furthermore the localization performance.

- **pseudo-annotation** provides a substitution of full supervision. Using global labels only for localization has seen large success to some extent. They allow identification of the most discriminative regions but are unable to recover full objects. Such partial, noisy, and uncertain pseudo-supervision is now deemed to be very useful to boost localization performance. It adds an extra-cheap supervision at the disposal of WSOL methods. However, they should be used with care since they could be very noisy which drives the model in the wrong direction or trap it in local solutions that predict similar pseudo-annotation.

- **decoupling classification and localization task.** Recent studies in WSOL showed that both tasks are shown to be antagonist: the localization task converges at the very early epochs then degrades later while the classification task converges toward the end of training. Recent works separate them by first training a classifier, then a localizer. The aim is to build a final framework that can yield best performance over both tasks. Note that recent successful works in WSOL task combine shallow features with pseudo-annotations while separating classification and localization tasks.

3 Experimental methodology

In this section we present the experimental procedure used to evaluate the performance of deep WSOL models. The aim of our experiments is to assess and compare their ability to accurately classify histology images, and localize cancerous ROIs.

In order to compare the localization performance of WSOL techniques on histology data, we selected different representative methods from both categories. From the **bottom-up** category, we consider the following methods: GAP (Lin et al., 2013), MAX-Pool (Oquab et al., 2015), LSE (Sun et al., 2016), CAM (Zhou et al., 2016), HaS (Singh and Lee, 2017), WILDCAT (Durand et al., 2017), ACoL (Zhang et al., 2018c), SPG (Zhang et al., 2018d), Deep MIL (Ilse et al., 2018), PRM (Zhou et al., 2018), ADL (Choe and Shim, 2019), CutMix (Yun et al., 2019), TS-CAM (Gao et al., 2021), MAXMIN (Belharbi et al., 2022b), NEGEV (Belharbi et al., 2022a); while we consider the following methods from **top-down category**: GradCAM (Selvaraju et al., 2017), GradCAM++ (Chattopadhyay et al., 2018), SmoothGradCAM++ (Omeiza et al., 2019), XGradCAM (Fu et al., 2020), LayerCAM (Jiang et al., 2021).

Experiments are conducted on two public datasets of histology images which are described in **subsection 3.3.** Most of the public datasets are collected exclusively for classification or segmentation purposes (Daisuke and Shumpei, 2018) such as BreaKHis (Spanhol et al., 2016b) and BACH (Aresta et al., 2018) datasets. Very few datasets have both image-level and pixel-level annotation. The only dataset that we found that has both types of annotation is **GlaS** (subsection 3.3.1). Using a single dataset for evaluation could be insufficient to draw meaningful conclusions. Therefore, we created an additional dataset with the required annotations by using a protocol to sample image patches from WSIs of the CAMELYON16 dataset (subsection 3.3.2).

3.1 Protocol

In all our experiments, we follow the same experimental protocol in (Choe et al., 2020) which defines a clear setup to evaluate ROI localization obtained by a weakly supervised classifier. The protocol includes two main elements: model selection, and an evaluation metric at pixel level.

In a weakly supervised setup, model selection is a critical aspect. The considered learning scenario in our experiments
entails two main tasks: Classification and localization which are shown to be antagonist tasks (Belharbi et al., 2022c; Choe et al., 2020). While the localization task converges at the very early training epochs, the classification task converges at late epochs. Therefore, to yield a better localization model, an adequate model selection protocol is required. Following (Choe et al., 2020), considering a full validation set that is labeled only at global level, we randomly select few samples to be labeled additionally at pixel level. In particular, we select few samples per class to yield a balanced set. These few samples are used for model selection using localization metric. This selection is referred to as B−LOC selection. Model selection using full validation set using only classification metric using global labels is referred to as B−CL selection. We provide results on both selection methods to assess their impact on performance. All results are reported using B−LOC selection, unless specified otherwise. We present in the next section the evaluation metrics.

3.2 Performance measures

For each task, i.e., classification and localization, we consider their respective metric.

3.2.1 Classification task

We use standard classification accuracy CL,

\[
\text{CL} = 100 \times \frac{\text{correctly classified samples}}{\text{samples}} \% \text{,}
\]

where \text{correctly classified samples} is the total number of correctly classified samples, and \text{samples} is the total number of samples.

3.2.2 Localization task

The aim of WSOL task is to produce a score map which is as well the average since the step between thresholds is fixed. We report the percentage values of each component, with respect to a fixed threshold as follows,

\[
\text{TP}(\tau) = \frac{|\{s_{ij}^{(n)} \geq \tau\} \cap \{T_{ij}^{(n)} = 1\}|}{|\{T_{ij}^{(n)} = 1\}|} \text{,}
\]

\[
\text{FN}(\tau) = \frac{|\{s_{ij}^{(n)} < \tau\} \cap \{T_{ij}^{(n)} = 1\}|}{|\{T_{ij}^{(n)} = 1\}|} \text{,}
\]

\[
\text{FP}(\tau) = \frac{|\{s_{ij}^{(n)} \geq \tau\} \cap \{T_{ij}^{(n)} = 0\}|}{|\{T_{ij}^{(n)} = 0\}|} \text{,}
\]

\[
\text{TN}(\tau) = \frac{|\{s_{ij}^{(n)} < \tau\} \cap \{T_{ij}^{(n)} = 0\}|}{|\{T_{ij}^{(n)} = 0\}|} \text{,}
\]

where TP, FN, FP, TN are the true positive, false negative, false positive, and true negative, respectively. Each component can be represented as a graph with x-axis is the threshold \(\tau\). Similarly to \(\text{PxAP}\), we marginalize confusion matrix components over \(\tau\) by measuring the area under each component which is as well the average since the step between thresholds is fixed. We report the percentage values of each component,

\[
\text{TP*} := 100 \times \sum_{l} \text{TP}(\tau) \times (\tau - \tau_{-1}) \text{,}
\]

\[
\text{FN*} := 100 \times \sum_{l} \text{FN}(\tau) \times (\tau - \tau_{-1}) \text{,}
\]

\[
\text{FP*} := 100 \times \sum_{l} \text{FP}(\tau) \times (\tau - \tau_{-1}) \text{,}
\]

\[
\text{TN*} := 100 \times \sum_{l} \text{TN}(\tau) \times (\tau - \tau_{-1}) \text{.}
\]

3.3 Datasets

We describe in this section the two public datasets of histology images used in our experiments: GlaS for colon cancer, and CAMELYON16 for breast cancer.

\[^{4}\text{In all the experiments, we used } \tau \in [0, 1] \text{ with a step of 0.001 as in (Choe et al., 2020).}\]
3.3.1 GlaS dataset (GlaS)

It is a histology dataset for colon cancer diagnosis (Sirinukunwattana et al., 2017). It contains 165 images from 16 Hematoxylin and Eosin (H&E) histology sections and their corresponding labels. For each image, both pixel-level and image-level annotations for cancer grading (i.e., benign or malignant) are provided. The whole dataset is split into training (67 samples), validation (18 samples) and testing (80 samples) subsets. Among the validation set, 3 samples per class are selected to be fully supervised, i.e. 6 samples in total for B-LOC selection.

3.3.2 Camelyon16 dataset (CAMELYON16)

The dataset is composed of 399 WSI for detection of metastases in H&E stained tissue sections of sentinel auxiliary lymph nodes (SNLs) of women with breast cancer (Ehteshami Bejnordi et al., 2017). The WSIs are annotated globally to normal or metastases. The WSIs with metastases are further annotated at pixel-level to indicate regions of tumors. An example of a WSI is provided in Figure 6. Among the provided 399 WSIs, 270 are used for training, and 129 for test. The large size of the images makes their usage in this survey inconvenient. Therefore, we design a concise protocol to sample small sub-images for WSL with pixel-wise and image-level annotation. In summary, we sample sub-images of size 512×512 to form train, validation, and test sets (Fig.7). A detailed sampling protocol is provided in Appendix B. This protocol generates a benchmark containing a total of 48,870 samples: 24,348 samples for training, 8,858 samples for validation, and 15,664 samples for testing. Each sub-set has balanced classes. For B-LOC, we randomly select 5 samples per class from the validation set to be fully supervised, i.e., 10 samples in total.

3.3.3 Implementation details

The training of all methods is performed using SGD with 32 batch size (Choe et al., 2020), 1000 epochs for GlaS, and 20 epochs for CAMELYON16. We use weigh decay of $10^{-4}$. Images are resized to 256x256, and patches of size 224x224 are randomly sampled for training. Since almost all methods were evaluated on natural images, we can not use the reported best hyper-parameters in their original papers. For each method, we perform a search of the best hyper-parameter over the validation set, including the learning rate.

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5The Gland Segmentation in Colon Histology Contest: https://warwick.ac.uk/fac/sci/dcs/research/tia/glascontest

6The Cancer Metastases in Lymph Nodes Challenge 2016 (CAMELYON16): https://camelyon16.grand-challenge.org/Home

7Sample test_114 is discarded since the pixel level annotation was not provided. Therefore, the test set is composed of 128 samples with 48 samples with nodal metastases.
| Methods/Metric             | PxA (B–LOC) | VGG Inception | ResNet | Mean |
|---------------------------|-------------|---------------|--------|------|
| **Bottom-up WSOL**        |             |               |        |      |
| GAP (Lin et al., 2013)    | 58.5        | 57.7          | 56.2   | 57.4 |
| MAX-Pool (Oquab et al., 2015) | 58.5       | 57.1          | 46.2   | 53.9 |
| LSE (Sun et al., 2016)    | 63.9        | 62.8          | 59.1   | 61.9 |
| CAM (Zhou et al., 2016)   | 68.5        | 50.5          | 64.4   | 61.1 |
| Hu (Singh and Lee, 2017)  | 65.9        | 65.4          | 63.5   | 64.8 |
| WILDCAT (Durand et al., 2017) | 56.1  | 54.9          | 60.1   | 57.0 |
| ACoL (Zhang et al., 2018c) | 63.7        | 58.2          | 54.2   | 58.7 |
| SPG (Zhang et al., 2018b) | 63.6        | 56.3          | 51.4   | 57.7 |
| Deep MIL (Bae et al., 2018) | 66.6      | 61.8          | 64.7   | 64.3 |
| PRM (Zhou et al., 2018b)  | 59.8        | 53.1          | 62.3   | 58.4 |
| ADL (Choe and Shim, 2019) | 65.0        | 60.6          | 54.1   | 59.9 |
| CutMix (Yun et al., 2019b) | 59.9        | 50.4          | 56.7   | 55.6 |
| TS-CAM (Gao et al., 2021) | 54.5        | 57.8          | 55.1   | 52.8 |
| MAXMIN (Belharbi et al., 2022b) | 75.0   | 49.1          | 81.2   | 68.4 |
| NEGEV (Belharbi et al., 2022a) | 81.3       | 70.1          | 82.0   | 77.8 |
| **Top-down WSOL**         |             |               |        |      |
| GradCAM (Selvaraju et al., 2017) | 75.7   | 56.9          | 70.0   | 67.5 |
| GradCAM++ (Chatfield et al., 2018) | 76.1     | 65.7          | 70.7   | 70.8 |
| Smooth-GradCAM++ (Omejra et al., 2019) | 71.3   | 67.6          | 75.3   | 71.4 |
| XGradCAM (Fu et al., 2020b) | 73.7       | 66.4          | 62.6   | 67.5 |
| LayerCAM (Jiang et al., 2021) | 67.8       | 66.1          | 70.9   | 68.2 |
| **Fully supervised**      |             |               |        |      |
| U-Net (Ronneberger et al., 2015) | 96.8   | 95.4          | 96.4   | 96.2 |

Table 1: PxA performance over GlA$S$ and CAMELYON16 test sets. Model selection: B–LOC.

| Methods/Metric             | VGG Inception | ResNet | Mean |
|---------------------------|---------------|--------|------|
| **Bottom-up WSOL**        |               |        |      |
| GAP (Lin et al., 2013)    | 34.5          | 65.4   | 20.5 |
| MAX-Pool (Oquab et al., 2015) | 38.7       | 61.2   | 31.5 |
| LSE (Sun et al., 2016)    | 52.0          | 47.9   | 41.4 |
| CAM (Zhou et al., 2016)   | 34.5          | 65.4   | 20.5 |
| Hu (Singh and Lee, 2017)  | 42.3          | 57.6   | 31.4 |
| WILDCAT (Durand et al., 2017) | 37.6  | 62.3   | 33.2 |
| ACoL (Zhang et al., 2018c) | 28.3        | 71.6   | 11.1 |
| SPG (Zhang et al., 2018d) | 62.2          | 37.7   | 50.5 |
| Deep MIL (Bae et al., 2018) | 14.7        | 85.2   | 7.3  |
| PRM (Zhou et al., 2018b)  | 41.8          | 58.1   | 34.7 |
| ADL (Choe and Shim, 2019) | 41.3          | 58.6   | 33.6 |
| CutMix (Yun et al., 2019b) | 41.3        | 58.6   | 33.6 |
| TS-CAM (Gao et al., 2021) | 23.1          | 70.8   | 2.04 |
| MAXMIN (Belharbi et al., 2022b) | 57.4   | 42.5   | 41.8 |
| NEGEV (Belharbi et al., 2022a) | 52.3       | 47.6   | 42.5 |
| **Top-down WSOL**         |               |        |      |
| GradCAM (Selvaraju et al., 2017) | 28.3   | 71.6   | 11.1 |
| GradCAM++ (Chatfield et al., 2018) | 30.6        | 69.3   | 13.4 |
| Smooth-GradCAM++ (Omejra et al., 2019) | 31.3      | 68.6   | 17.0 |
| XGradCAM (Fu et al., 2020b) | 31.5        | 68.4   | 14.9 |
| LayerCAM (Jiang et al., 2021) | 35.4       | 64.5   | 23.6 |
| **Fully supervised**      |               |        |      |
| U-Net (Ronneberger et al., 2015) | 89.8   | 10.1   | 11.6 |

Table 2: Confusion matrix performance over GlA$S$ test set. Model selection: B–LOC.

For the methods (Belharbi et al., 2022a,b), we set part of the hyper-parameters as described in their papers since they were evaluated on the same histology datasets. For each method, the number of hyper-parameters to tune ranges from one to six. We use three different common backbones (Choe et al., 2020): VGG16 (Simonyan and Zisserman, 2015), InceptionV3 (Szegedy et al., 2016), and ResNet50 (He et al., 2016). For TS-CAM method (Gao et al., 2021), we use DeiT-based architectures (Touvron et al., 2021); DeiT-T (t), DeiT-S (s), DeiT-B (b). We use U-Net (Ronneberger et al., 2015) with full
We report localization performance (mAP) of all methods in Table 1 over both datasets GLaS and CAMELYON16. Overall, we note a discrepancy in performance between difference backbones. In addition, CAMELYON16 dataset seems to be more challenging than GLaS dataset. Note that methods that were designed for histology images such as MAXMIN (Belharbi et al., 2022b) and NEGEV (Belharbi et al., 2022a) yield the best localization performance compared to generic methods that were designed and evaluated on natural images. Top-down methods, such GradCAM++ (Chattopadhyay et al., 2018) and LayerCAM (Jiang et al., 2021) have shown to be more efficient than bottom-up methods over GLaS. Although, Deep MIL method (Ilse et al., 2018) yielded interesting results. Over CAMELYON16, both categories yielded poor results.

The overall results show also that there is a large performance gap between learning with weak supervision (global label in this case) and full supervised method. This highlights the difficulty of histology images compared to natural images.

We inspect as well the confusion matrix to better assess the pixel-wise predictions on both datasets GLaS (Table 2) and CAMELYON16 (Table 3). The first observation is the high false negative rate where large part of ROI are considered background. This metric goes up to ~93% over GLaS and 100% over CAMELYON16. This indicates that WSOL methods tend to under-activate by highlighting only small part of the object and missing the rest. Under-activation is a common behavior in WSOL method over natural images (Choe et al., 2020) which increases false negatives. We observe a new trend that is high false positive which is less common in WSOL (Choe et al., 2020). This is caused by over-activation on entire image including ROI and background. The visual similarity between foreground/background regions is the source of this issue making the model unable to discriminate between both regions. In average, false positives are much more frequent in CAMELYON16 than GLaS. However, in both datasets, false negative is much more higher than false positives.

These results suggest that when dealing with histology images, WSL method can exhibit two behaviors, either under-activate or over-activate leading to high false negatives or negatives. Both drawbacks should be considered when designing WSOL methods for this type of data. We provide visual results of both behaviors in Appendix C. In histology literature, two
In WSOL task, thresholding is required (Choe et al., 2020) to obtain a mask of a specific ROI. All the localization performance reported in this work are marginalized over a set of thresholds for the purpose of a fair comparison (Choe et al., 2020). It has been shown that the values of threshold is critical for the localization performance (Choe et al., 2020). In practice, for a test sample, one needs to threshold the CAM to yield a discrete localization of ROI\(^8\). Ideally, the value of threshold should not have a major impact on the ROI localization. However, it is not the case for WSOL. Evaluations on natural images (Belharbi et al., 2022c; Choe et al., 2020) have shown that localization performance from CAMs obtained in weakly-supervised setup are strongly tied to thresholds. We perform similar analysis to the variation of localization performance with respect to the threshold in Figure 8. We observe a steep decline in performance when increasing the threshold similarly to results obtained in (Belharbi et al., 2022c; Choe et al., 2020). This highlights again the dependency of localization to the threshold, and also indicates that optimal thresholds are concentrated near zero similarly to (Belharbi et al., 2022c; Choe et al., 2020). These results also suggest that CAM’s activations distribution has a single mode located near zero as the results in (Belharbi et al., 2022c; Choe et al., 2020). This makes finding an optimal threshold difficult, therefore, it makes CAMs sensitive to thresholding which reflects the uncertainty in CAMs. Ideally, the activation distribution is expected to be bimodal: background mode near zero, and foreground mode near one. This makes separating between foreground and background easier and less sensitive to threshold such as in full supervised method. CAM’s vulnerability to thresholding is still an open issue in WSOL (Belharbi et al., 2022c; Choe et al., 2020), which should be considered in future design of WSOL methods for general purposes including applications on histology data.

Results in Figure 8 also showed that there is still a large performance gap between WSOL and fully supervised methods. This gap is much more large in CAMELYON16 dataset.

### 4.3 Importance of model selection

Typically, training a model for localization with image class as weak supervision is done without having access to any localization information. This means that only classification information can be used to perform model selection using early stopping via a validation set for instance. However, it has been shown that classification and localization tasks are antagonist (Belharbi et al., 2022c; Choe et al., 2020). This implies that model selection via localization (B−LOC) leads to good localization and more likely poor classification. On the other hand, selection using classification (B−CL) yields good classification and more likely poor localization as observed empirically in (Belharbi et al., 2022c; Choe et al., 2020).

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\(^8\)Activations of CAMs can be also exploited visually by the user to determine ROI and manually inspect them.
Figure 9: Impact of model selection (B-LOC: orange. vs. B-CL: blue) over test localization (PxA) performance. Each point indicates the epoch (x-axis) at which the best model is selected and its corresponding localization performance (y-axis). Large circles indicate the average over all WSOL methods. Top: GLaS. Bottom: CAMELYON16.

The authors in (Choe et al., 2020) suggested a standard protocol for WSOL where few samples of validation set are fully labeled, i.e. they have localization annotation. Such subset is used for model selection using localization (B-LOC) performance. While being unrealistic, this protocol allows a fair comparison between methods by removing user-bias from selection.

We show in Figure 9 the impact of model selection on localization performance. We observe two main trends. First, localization performance converges at the very early epochs while classification converges toward the end. This indicates that localization performance reaches its peak early then degrades with long training epochs. The opposite can be said about classification. This results is consistent with the findings in (Belharbi et al., 2022c; Choe et al., 2020) over natural images. A second important observation is that, on average, using localization information for model selection yields slightly better localization performance compared to when using classification metric for model selection. Note that the total average gap varies on both datasets with ~2% for GLaS, and ~8% for CAMELYON16. This suggests that difficult datasets may benefit more from localization selection. The details of localization performance difference is reported in Table 4.

In addition, we inspected the impact of mode selection over classification performance in Table 5. We observe that model selection using classification metric (B-CL) yields better classification performance than when using localization for selection (B-LOC).

These results go in the same direction as in (Choe et al., 2020). This confirms again that classification and localization under a weakly-supervised setup are more likely to be antagonist. This is another issue to consider when designing WSL methods.

The issue of model selection in WSOL has been highlighted in (Choe et al., 2020) including its impact on localization and classification performance on natural images. Similar behavior is observed here on histology dataset. There is no clear solution to this issue. Most research in WSOL aims to improve state-of-the-art performance in localization. Works in (Belharbi et al., 2022a,c; Zhang et al., 2020a) propose to separate localization from classification task. First, they train a classifier to get the best performance. Then, using information from classifier, a localizer is trained. This strategy allows to obtain a final framework that yields best classification and localization performance.

5 Conclusion and future directions

Training deep models for ROI localization in histology images requires costly dense annotation. In addition, such labeling is performed by medical experts. Weakly supervised object localization framework provides different techniques for low-cost training of deep models. Using only image-class annotation, WSOL methods can be trained to classify an image and yield localization of ROI via CAMs. Despite its success, WSOL framework still faces a major challenge which is to correctly transfer image-class label to pixel-level. Moreover, histology images present additional challenges compared to natural images including their size, stain variation, and labels ambiguity. Most importantly, ROI in histology data are less salient which makes spotting them much more difficult. This easily exposes WSOL models to false positive/negatives.

Since in a real weakly supervised application, we do not have any localization information.
Table 4: Comparison of localization performance (PrAP) with respect to model selection method: B-LOC/B-CL over GlaS and CAMELYON16 test sets. Colors: CL (B-LOC) < CL (B-CL) meaning that localization performance PrAP obtained using B-LOC is worse than when using B-CL. CL (B-LOC) > CL (B-CL) meaning that localization performance obtained using B-LOC is better than when using B-CL. Better visualized with color. NEGEV method (Belharbi et al., 2022a) is not considered in this table because the classifier is pretrained and frozen. Only B-LOC is used for model selection.

Therefore, the application of WSOL techniques to histology data raises additional several challenges.

In this work, we have presented a review of several deep WSOL methods between the year of 2013 and early 2022. We divided them into two main categories based on the information flow in the model: bottom-up, and top-down methods. The latter have seen limited progress. However, bottom-up methods are the current driving force of WSOL task. They have seen several major changes that brought more progress to this task. Early works focused on designing different spatial pooling functions. However, quickly these methods reached limited performance and unveiled a major limitation to CAMs that is under-activation. Subsequent works aimed to alleviate this issue and recover complete object using different techniques including: perturbation, self-attention, shallow features, pseudo-annotation, and tasks decoupling. Recent state-of-the-art methods combine several of these techniques.

To assess localization and classification performance of WSOL techniques over histology data, we selected representative methods in our taxonomy for experimentation. We evaluated them over two histology datasets; one for colon cancer (GlaS) and a second dataset for breast cancer (CAMELYON16) using standard protocol for WSOL task (Choe et al., 2020). Overall, the results indicate poor localization performance particularly for generic methods that were designed and evaluated over natural images. Methods designed considering histology data challenges yielded good results. In general, all methods suffer from high false positive/negative localization. Furthermore, our analysis showed the following issues:

- **under-activation** where CAMs activate only over small discriminative region which increases false negatives. This is a documented behavior over natural images.

- **over-activation** where CAMs activate over entire image which increases false positives. This is a new behavior of WSOL which is mostly caused by the similarity between foreground and background regions. This makes discrimination between both region difficult. Common strategies to reduce both issues are: 1) usage of priors over regions size (Belharbi et al., 2022b). Size of both foreground and background in an image is constrained to be as large as possible. However, the analytical solution to their constraint is reached when each regions covers half of the image. Their results showed that such trivial solution does not occur in practice due to other competing constraints. 2) usage of pseudo-annotations (Belharbi et al., 2022a). Authors used
Table 5: Comparison of classification accuracy (CL) with different model selection method: B-LOC/B-CL on GlaS and CAMELYON16 test sets. Colors: CL (B-LOC) < CL (B-CL) meaning that classification accuracy obtained using B-LOC is worse than when using B-CL. CL (B-LOC) > CL (B-CL) meaning that classification accuracy obtained using B-LOC is better than when using B-CL. Better visualized with color. NEGEV method (Belharbi et al., 2022a) is not considered in this table because the classifier (CAM (Zhou et al., 2016)) is pretrained and frozen. Only B-LOC is used for model selection.

| Methods / Metric       | VGG Inception ResNet | Mean | VGG Inception ResNet | Mean |
|------------------------|----------------------|------|----------------------|------|
| **WSOL**               |                      |      |                      |      |
| GAP (Lin et al., 2013) | 49.2/98.7            |      | 87.5/95.0            |      |
| MAX-Pool (Oquab et al., 2015) | 97.5/97.5            |      | 75.9/96.5            |      |
| LSE (Sun et al., 2016) | 92.5/93.7            |      | 90.4/93.7            |      |
| CAM (Zhou et al., 2016) | 100/100              |      | 82.6/95.0            |      |
| Huš (Singh and Lee, 2017) | 96.2/92.5            |      | 81.9/95.0            |      |
| WILDCAT (Durand et al., 2017) | 50.0/100             |      | 79.9/95.0            |      |
| ACoL (Zhang et al., 2018c) | 100/92.5             |      | 80.4/95.0            |      |
| SPG (Zhang et al., 2018b) | 53.7/83.7            |      | 59.9/91.6            |      |
| Deep MIL (Ilse et al., 2018) | 96.2/100             |      | 90.4/95.0            |      |
| PRM (Zhou et al., 2018b) | 96.2/100             |      | 82.0/94.1            |      |
| AIDL (Choi and Shim, 2019) | 100/100              |      | 90.4/96.2            |      |
| CatMx (Yun et al., 2019) | 100/88.7             |      | 95.4/93.3            |      |
| TS-CAM (Gao et al., 2021) | 100/100              |      | 84.1/95.0            |      |
| MAXMIN (Belharbi et al., 2022b) | 83.7/100             |      | 76.2/98.7            |      |

| **Top-down WSOL**      |                      |      |                      |      |
| GraddGrad (Selvaraju et al., 2017) | 97.5/100             |      | 93.7/96.2            |      |
| GradCam++ (Chattopadhay et al., 2018) | 97.5/100             |      | 40.2/86.6            |      |
| Smooth-GradCam++ (Omeiza et al., 2019) | 100/100              |      | 85.4/88.7            |      |
| XGradCAM (Fu et al., 2020) | 100/100              |      | 83.3/89.5            |      |
| LayerCAM (Jiang et al., 2021) | 100/100              |      | 82.1/86.6            |      |

- **sensitivity to thresholding** which is another documented issue for CAMs over natural images which occurred over histology data as well. A typical solution is to push CAMs activation to be more certain. However, altering CAMs distribution could deteriorate classification performance. A possible solution is to separate classification scoring function from CAMs such as in the architecture proposed in (Belharbi et al., 2022a,c).

- **model selection.** Using only classification accuracy allowed to select models that have high classification performance but poor localization. On the other hand, using localization performance for model selection yielded the opposite case. This is a common issue in WSOL task. Recent works suggested to separate both tasks to obtain a framework that yields best performance for both tasks. The proposed architecture in (Belharbi et al., 2022a) holds a key solution to this issue. First a classifier is trained then frozen. Next, the localized is trained. When trained properly, the final model is expected to yield best performance in both tasks.

Our final conclusion in this work is that the localization performance obtained with WSOL methods with application to histology data is still behind full supervision performance. They are still unable to accurately localize ROI mainly due to their non-saliency aspect. We cited several key issues to be considered when designing future WSOL techniques for histology data in order to close the performance gap between weakly and fully supervised methods.

A Hyper-parameter search

We present in Table 6 the general hyper-parameters used for all methods. Table 7 holds hyper-parameters for specific methods.
Table 6: General hyper-parameters. Notation in this table follows the same notation in the original papers.

| Hyper-parameter                | Value                        |
|-------------------------------|------------------------------|
| Model full sup.               | U-Net                        |
| Backbones                     | VGG16, InceptionV3, ResNet50.|
| Optimizer                     | SGD                          |
| Nesterov acceleration         | True                         |
| Momentum                      | 0.9                          |
| Weight decay                  | 0.0001                       |
| Learning rate decay           | \(GlaS: 0.1\) each 250 epochs.|
| Mini-batch size               | 32                           |
| Random flip                   | Horizontal/vertical random flip|
| Random color jittering        | Brightness, contrast, and saturation at 0.5 and hue at 0.05 |
| Image size                    | Resize image to \(225 \times 225\). Then, crop random patches of \(224 \times 224\). |
| Learning epochs               | \(GlaS: 10000\), CAMELYON16: 20 |

Table 7: Per-method hyper-parameters. Notation in this table follows the same notation in the original papers.

| Hyper-parameter                | Value                        |
|-------------------------------|------------------------------|
| LSE (Sun et al., 2016)        | \(q \in \{1, 2, 3, 4, 5, 6, 7, 8, 9, 10\}\) |
| HaS (Singh and Lee, 2017)     | Grid size \(\in \{8, 16, 32, 44, 56\}\), Drop rate \(\in \{0.2, 0.3, 0.4, 0.5, 0.6\}\) |
| WILDCAT (Durand et al., 2017) | \(\alpha \in \{0.1, 0.6\}\) |
| WILDCAT (Durand et al., 2017) | \(k_{max} \in \{0.1, 0.3, 0.5, 0.6, 0.7\}\), \(k_{min} \in \{0.1, 0.2, 0.3\}\), Modalities = 5 |
| ACoL (Zhang et al., 2018c)    | \(\delta \in \{0.5, 0.6, 0.7, 0.8, 0.9\}\) |
| ACoL (Zhang et al., 2018c)    | \(\delta_a \in \{0.5, 0.7\}\), \(\delta_t \in \{0.01, 0.05, 0.1\}\), \(\delta_{a2} \in \{0.01, 0.05, 0.1\}\), \(\delta_{at} \in \{0.5, 0.6, 0.7\}\), \(\delta_{at2} \in \{0.01, 0.05, 0.1\}\) |
| SPG (Zhang et al., 2018d)     | \(r \in \{3.5, 7, 9, 11, 13\}\), Kernel stride \(\in \{1, 3.5, 7, 9, 11, 13\}\) |
| ADL (Cho et al., 2019)        | \(\gamma \in \{0.75, 0.85, 0.90\}\) |
| CutMix (Sun et al., 2019)     | \(\alpha = 1.0\) |
| MAXMIN (Belharbi et al., 2022b) | \(\lambda \in \{0.5, 0.6, 0.7, 0.8, 0.9, 1.0\}\) |
| NEGEV (Belharbi et al., 2022a) | Same as (Belharbi et al., 2022a) |

B  CAMELYON16 protocol for WSL

This appendix provides details on our protocol of creating a WSOL benchmark from CAMELYON16 dataset (Ehteshami Bejnordi et al., 2017). Samples are patches from WSIs, and each patch has two levels of annotation:

- **Image-level label** \(y\): the class of the patch, where \(y \in \{\text{normal}, \text{metastatic}\}\).
- **Pixel-level label** \(Y = \{0, 1\}^{H \times W}\): a binary mask where the value 1 indicates a metastatic pixel, and 0 a normal pixel. For normal patches, this mask will contain 0 only.

First, we split CAMELYON16 dataset into train, validation, and test set at **WSI-level**. This prevent patches from the same WSI to end up in different sets. All patches are sampled with the highest resolution from WSI—i.e. level = 0 in WSI terminology—. We present in the following our methodology of sampling metastatic and normal patches.

**Sampling metastatic patches.** Metastatic patches are sampled only from metastatic WSIs around the cancerous regions. Sampled patches will have image-level label, and a pixel-level label. The sampling follows these steps:

1. Consider a metastatic WSI.
2. Sample a patch \(x\) with size \((H, W)\).
3. Binarize the patch into \(x^b\) mask using Otsu method (Otsu, 1979). Pixels with value 1 indicate tissue.
4. Let \(p^x_t\) be the tissue percentage within \(x^b\). If \(p^x_t < p_t\), discard the patch.
5. Compute the metastatic binary mask \(Y\) of the patch \(x\) using the pixel-level annotation of the WSI (values of 1 indicate a metastatic pixel).
6. Compute the percentage \(p^x_m\) of metastatic pixels within \(Y\).
7. If \(p^x_m < p_0\), discard the patch. Else, keep the patch \(x\) and set \(y = \text{metastatic}\) and \(Y\) is its pixel-level annotation.

We note that we sample all possible metastatic patches from CAMELYON16 using the above approach. Sampling using such approach will lead to a large number of metastatic patches with high percentage of cancerous pixels (patches sampled from the center of the cancerous regions). These patches will have their binary annotation mask \(Y\) full of 1. Using these patches will shadow the performance measure of localization of cancerous regions. To avoid this issue, we propose to perform a calibration of the sampled patches in order to remove most of such patches. We define two categories of metastatic patches:

1. **Category 1**: Contains patches with \(p_0 \leq p^x_m \leq p_1\). Such patches are rare, and contain only small region of cancerous pixels. They are often located at the edge of the cancerous regions within a WSI.
2. **Category 2**: Contains patches with \(p^x_m > p_1\). Such patches are extremely abundant, and contain a very large
region of cancerous pixels (most of the time the entire patch is cancerous). Such patches are often located inside the cancerous regions within a WSI.

Our calibration method consists in keeping all patches within Category 1, and discarding most of the patches in Category 2. To this end, we apply the following sampling approach:

1. Assume we have \( n \) patches in Category 1. We will sample \( n \times p_n \) patches from Category 2, where \( p_n \) is a predefined percentage.
2. Compute the histogram of the frequency of the percentage of cancerous pixels within all patches. Assuming a histogram with \( b \) bins.
3. Among all the bins with \( p_x > p_1 \), pick uniformly a bin.
4. Pick uniformly a patch within that bin.

This procedure is repeated until we sample \( n \cdot p_n \) patches from Category 2.

In our experiments, patches are not overlapping. We use the following configuration: \( p_0 = 20\% \), \( p_1 = 50\% \), \( p_t = 10\% \), \( p_n = 1\% \). The number of bins in the histogram is obtained by dividing the interval \([0, 1]\) with a delta of 0.05. These hyper-parameters are not validated to optimize the performance of the models but were set in a reasonable way to simple automatically consistent and unbalanced patches without the need to manually check the samples. Patch size is set to \( 512 \times 512 \). Figure 10 illustrates an example of metastatic patches and their corresponding masks.

Let us consider a set (train, validation, or test) at patch level. We first pick the corresponding metastatic patches from the metastatic WSI, assuming \( n_m \) is their total number. Assuming there is \( h \) normal WSIs in this set, we sample the same number of normal patches as the total number of metastatic ones. In order to mix the patches from all the normal WSI, we sample \( \frac{n_m}{h} \) normal patches per normal WSI. In our experiment, we use the same setup as in the case of sampling metastatic patches: \( p_t = 10\% \). Figure 11 illustrates an example of normal patches.

\[ \text{Figure 11: Example of normal patches with size } 512 \times 512 \text{ sampled from CAMELYON16 dataset (WSI: normal_001.tif).} \]

C Visual results

We provide in this section visual results of localization of different methods using ResNet50 backbone: Figure 12, and Figure 13 for GlaS test set; and Figure 14 and Figure 15 for CAMELYON16 test set.

Sampling normal patches. Normal patches are sampled only from normal WSI. A normal patch is sampled randomly and uniformly from the WSI (without repetition nor overlapping). If the patch has enough tissue \( (p_x^b \geq p_t) \), the patch is accepted. The measure of tissue mass is performed at level \( = 6 \) where it is easy for the OTSU binarization method to split the tissue from the background. We double-check the tissue mass at level \( = 0 \).
Figure 12: CAM predictions over \textbf{benign} test samples for GLaS. Ground truth ROIs are indicated with red mask highlighting glands. In all prediction, strong CAM’s activations indicate glands. Backbone: ResNet50.
Figure 13: Predictions over **malignant** test samples for GLaS. Ground truth ROIs are indicated with red mask highlighting glands. In all prediction, strong CAM’s activations indicate glands. Backbone: ResNet50.
Figure 14: Predictions over **normal** test samples for CAMELYON16. Ground truth ROIs are indicated with red mask highlighting metastatic regions. In all prediction, strong CAM’s activations indicate metastatic regions. Backbone: ResNet50.
Figure 15: Predictions over metastatic test samples for CAMELYON16. Ground truth ROIs are indicated with red mask highlighting metastatic regions. In all prediction, strong CAM’s activations indicate metastatic regions. Backbone: ResNet50.
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