Not-so-supervised: a survey of semi-supervised, multi-instance, and transfer learning in medical image analysis
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Abstract—Machine learning (ML) algorithms have made a tremendous impact in the field of medical imaging. While medical imaging datasets have been growing in size, a challenge for supervised ML algorithms that is frequently mentioned is the lack of annotated data. As a result, various methods which can learn with less/other types of supervision, have been proposed. We review semi-supervised, multiple instance, and transfer learning in medical imaging, both in diagnosis/detection or segmentation tasks. We also discuss connections between these learning scenarios, and opportunities for future research.

Keywords machine learning, medical imaging, computer aided diagnosis, semi-supervised learning, multiple instance learning, transfer learning, multi-task learning

I. INTRODUCTION

Machine learning has become very important in medical image analysis. Tasks such as segmentation, where each pixel or voxel in an image is assigned to a different anatomical structure or tissue type, and computer-aided diagnosis where a category label for an entire image is predicted, are now almost exclusively done with machine learning methods.

A problem that is often cited when applying machine learning methods to medical images, is the lack of labeled data [Litjens et al., 2017] [Weese and Lorenz, 2016], even if larger sets of unlabeled data may be more widely available. An important reason for this is the sheer difficulty of collecting the labels. Manual labeling of the images is expensive and/or time-consuming process, and such labels might not be needed in clinical practice, therefore reducing the amount of labeled data only to research studies. Another issue is that, even if labeled data is collected, it is not readily available to other researchers.

The lack of labeled data motivates approaches which go beyond traditional supervised learning by using other types of data and/or labels that might be more easily accessible. These approaches include semi-supervised learning, multiple instance learning and transfer learning, although many other terms exist to describe these approaches. Papers within one of these learning scenarios seem to be aware of other related literature, and surveys are emerging, such as [Quellec et al., 2017].

However, it seems that there is little interaction between the scenarios, which is a missed opportunity, since their goals are related. With this survey, we aim to provide an overview of the learning scenarios, describe their connections, identify gaps in the current approaches, and provide several opportunities for future research.

A. Selection of papers

An initial selection of papers was created by VC, who has been receiving Google Scholar alerts for the terms “multiple instance learning” and “transfer learning” since 2014, and screening these for medical imaging papers. These papers were used to identify other relevant publications. In the event of multiple similar papers, only the latest paper was included. Only papers which became available online before 2018 were included.

This survey does not cover approaches which rely on interaction with the annotator, such as active learning or crowdsourcing, in detail. We focus on machine learning approaches which can be used even if there is no possibility of acquiring additional labels. We focus on classification tasks within medical image analysis, for diagnosis, detection or segmentation purposes.

It is our intention to provide an overview how different learning scenarios are being used rather than a full summary of all related papers. It is therefore likely that not all relevant papers were identified with our strategy. We are open to receiving suggestions (by email to the corresponding author) for other relevant literature to include while this paper is only available as a preprint.

II. OVERVIEW OF TECHNIQUES

In this section we provide an quick overview of the learning scenarios and summarize the notation used throughout this survey. We also provide examples of each type of learning scenario, based on the application of classifying emphysema, a sign of chronic obstructive pulmonary disease (COPD) in chest computed tomography (CT) images. For readability, we provide a list of notation and acronyms used throughout the paper in Tables I and II.

In supervised learning, we have a labeled training set \( S_L = \{(x_i, y_i), i = 1, \ldots, N_S\} \) where \( x_i \in \mathcal{R}^m \) is an instance (described by a \( m \)-dimensional feature vector) and \( y_i \in \{0, 1\} \) is its label. We want to use this data to train a classifier \( f : \mathcal{R}^m \rightarrow \{0, 1\} \) which can classify unlabeled samples from a previously unseen test set \( T = \{z_i\} \). For example, the instances are patches in a chest CT image, and they are labeled as emphysema or as normal tissue. At test time, we want to classify all patches in a previously unseen scan as emphysema or not. This example is illustrated in Fig. II(a).

In semi-supervised learning (SSL), in addition to the training set we have an unlabeled set of data \( S_U \). We want to use
this set to improve the predictions of the classifier \( f \) on \( T \). For example, the supervised problem above can be extended with patches from chest CT images, which have not been manually labeled by experts. This scenario is covered in Section III and illustrated in Fig. 1(b).

In multiple instance learning (MIL), the training set itself consists of sets (bags) of instances, i.e. \( S_L = \{ (S^i, Y^i) | i = 1, \ldots, N_S \} \) where \( X_i = \{ x_{ij} | j = 1, \ldots, N_i \} \) and \( Y_i \in \{ 0, 1 \} \). We assume that the instances \( \{ x_{ij} \} \) have labels \( y_{ij} \), and that they are related to the bag label by an aggregation function \( Y_i = g(\{ y_{ij} \}) \). The test set also consists of bags, \( T = \{ X^i_T, i = 1, \ldots, N_T \} \), which are unlabeled. For example, this situation can occur if the radiologist only labeled an entire CT scan as containing emphysema or not, but has not indicated its locations.

Next the goal can be two-fold: to classify the test bags \( X^i_T \), and/or to classify the test instances \( x_{ij} \). In our example, the bag classifier would predict whether a patient has any emphysema (i.e. has COPD or not), whereas the instance classifier would classify individual patches to detect the emphysema in the image. This scenario is covered in Section IV and illustrated in Fig. 1(c).

In the scenarios above, we assume that the training and test data originate from the same distribution, i.e. \( S = T \). This means \( P(x^i, y) = P(x^j, y) \) for supervised learning and \( P(x^S, Y^S) = P(x^T, Y^T) \) for MIL. However, this is not always the case, creating a transfer learning (TL) scenario. Instead we assume to have a source datasets \( S_L \) and a test, or target set \( T \), where \( P(S) \neq P(T) \). For example, this can occur when different scanning protocols are used to create \( S \) and \( T \), and emphysema patches in these datasets occupy different parts of the feature space. The goal is to train a classifier using \( S \), and possibly using either the unlabeled test data \( T \), and/or labeled data from the target domain \( T_L \). This scenario is covered in Section V and illustrated in Fig. 1(d). As we discuss later, this scenario is not limited to the case where there are differences in the feature distributions.

In Section VI we discuss the trends within these learning scenarios, the gaps in the current research, and the opportunities and challenges for future research.

### III. SEMI-SUPERVISED LEARNING

In the semi-supervised learning scenario, there are two sets of samples: labeled samples \( S_L \) and unlabeled samples \( S_U \). The goal is to use the samples in \( S_U \) to improve the classifier \( f \). For example, when classifying emphysema vs health patches, the scans that have been annotated are used to create a set of labeled patches, while the scans without annotations can be used to create a large unlabeled set of patches. We can distinguish two goals in SSL: predicting labels for future data (inductive SSL) and predicting labels for the already available unlabeled samples (transductive SSL) [Zhu and Goldberg 2009].

Typically semi-supervised approaches work by making additional assumptions about the available data [Chapelle et al. 2006, Zhu and Goldberg 2009]. These include the smoothness assumption, i.e. samples close together in feature space are likely to be from the same class, the cluster assumption, i.e. samples in a cluster are likely to be from the same class, and the low density assumption, i.e. class boundaries are likely to be in low density areas of the feature space.

Many semi-supervised approaches therefore proceed with exploiting such assumptions. A popular method called self-training propagates labels from the labeled to the unlabeled data, and then using the larger, newly labeled set for training. This can also be an iterative process, where the classifier iterates between finding the best possible labels for the unlabeled samples, retraining itself, and so forth. This approach assumes that the method’s high confidence predictions are correct, which is likely to be the case with the cluster assumption. A related approach is co-training, where classifiers are trained with independent sets of features, and the classifiers rely on each other for estimating the confidence of their predictions.

Other popular methods include methods which regularize the classifier, such as graph-based methods and semi-supervised support vector machines (SVMs). An overview of methods and corresponding assumptions can be found in [Zhu and Goldberg 2009].

When the initial assumptions do not hold, there is a risk of performing worse than a supervised approach [Cozman and Cohen 2006] [Zhu and Goldberg 2009]. More recent approaches that do not make additional assumptions about the data, and instead use assumptions already present in the classifier [Loog and Jensen 2013, Krijthe and Loog 2017]. This can be achieved by linking parameter estimates (such as mean and variance of the samples) based on labeled samples, to those based on all available samples.

### TABLE I: Notation used throughout the paper

| Source domain | \( S \) |
| Target domain | \( T \) |
| Labeled training set | \( S_L \in S \) |
| Unlabeled test set | \( T \in T \) |
| Unlabeled source data | \( S_U \in S \) |
| Labeled target data | \( T_L \in T \) |
| Training instance | \( x_i^S \) |
| Test instance | \( x^T_i \) |
| Instance label | \( y_i \) |
| Training bag | \( X_i^S = \{ x_{ij}^S, j = 1, \ldots, N_i \} \) |
| Test bag | \( X^T_i = \{ x_{ij}^T, j = 1, \ldots, N_i \} \) |
| Bag label | \( Y_i \) |

### TABLE II: Acronyms used throughout the paper

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ML</td>
<td>machine learning</td>
</tr>
<tr>
<td>SSL</td>
<td>semi-supervised learning</td>
</tr>
<tr>
<td>MIL</td>
<td>multiple instance learning</td>
</tr>
<tr>
<td>TL</td>
<td>transfer learning</td>
</tr>
<tr>
<td>MTL</td>
<td>multi-task learning</td>
</tr>
<tr>
<td>SVM</td>
<td>support vector machine</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>MCI</td>
<td>mild cognitive impairment</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DR</td>
<td>diabetic retinopathy</td>
</tr>
<tr>
<td>MR</td>
<td>magnetic resonance</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
</tbody>
</table>

TABLE II: Acronyms used throughout the paper
Fig. 1: Learning scenarios, illustrated by a task of classifying healthy (green) vs emphysema (red) tissue in chest CT images. Annotations are made for presentation purposes only and do not necessarily reflect ground truth. **Top left:** Supervised learning, only healthy and abnormal patches are available. **Top right:** Semi-supervised learning (Section III). In addition to healthy and abnormal patches, unlabeled patches are available. **Bottom left:** Multiple instance learning (Section IV). Labeled patches are not available, but subject-level labels (whether any abnormal patches are present) are. **Bottom right:** Transfer learning (Section V). Labeled patches are available, but for a different domain (here illustrated by different visual characteristics) than in the test set.
A. SSL in medical imaging

SSL is a naturally occurring scenario in medical imaging, both in segmentation and diagnosis tasks. In segmentation methods, an expert might label only a part of the image, leaving many samples unlabeled. In computer-aided diagnosis, there might be ambiguity about the label of a subject, rather than adding these subjects to the training set or removing them completely, they can still be used to improve the classifier. For example, in classification of Alzheimer’s disease (AD), subjects with mild cognitive impairment (MCI) which may or may not develop AD later, are sometimes considered as unlabeled data [Filipovych et al., 2011, Batmanghelich et al., 2011].

The contributions are summarized in Table III. Overall there are two main directions. In the first, papers use a self-training or co-training approach for segmentation purposes. We discuss these in Section III-B. In the second, papers use the unlabeled data to regularize the classifier via graph-based methods or SVMs. These approaches are used both for segmentation and diagnosis tasks. We discuss these papers in Section III-C.

B. Self-training and co-training

A popular approach to SSL in medical imaging is label propagation via self-training. The general idea is as follows. A classifier is first trained on the labeled samples. The trained classifier then classifies the unlabeled samples. These samples, or a subset of these samples, are then added to the training set. This process is repeated several times.

The surveyed papers differ in how they select the subset of unlabeled samples to add to the labeled data. Several papers choose an active learning approach, where expert interactions is needed to verify the labels [Parag et al., 2014, Su et al., 2016]. As mentioned in the introduction, we do not in detail address active learning, as the performance of these methods is going to depend on the expert.

Other papers measure the uncertainty or confidence of the classifier based on the output (posterior probability) of the classifier itself, and possibly additional classifiers. Wang et al. [2014] add samples with a confidence above a user-selected threshold to the training set. Additional classifiers can be used as well, in which the method falls under co-training. For example, for skull segmentation, Iglesias et al. [2010] use two conventional tools and their own classifier, to classify all the unlabeled pixels. The pixels for which the conventional tools agree, but their own classifier is not confident, are added to the labeled set. A similar strategy is used by van Rikxoort et al. [2010] for classifying tuberculosis patterns in chest CT, but with simple classifiers as experts.

Self-training is popular for segmentation, for propagating labels between pixels/voxels. It is used in the brain [Iglesias et al., 2010, Meier et al., 2014, Wang et al., 2014, Dittrich et al., 2014], retina [Gu et al., 2017], heart [Bai et al., 2017] and several other applications. Self-training is less common for computer-aided detection or diagnosis applications. In the surveyed papers, van Rikxoort et al. [2010] classify volumes of interest in chest CT and Singh et al. [2011] classify cell nuclei, but in both cases the sample size is in the thousands. This suggests that self-training is particularly prone to degrade performance if the sample size is low.

A few works investigate how the sample size affects performance. Iglesias et al. [2010] look at both the amount of labeled and unlabeled data in a skull segmentation task. The show that increasing the number of scans that voxels are sampled from, improves performance, even if the number of voxels used to train the classifier stays the same. They also show that as the diversity of labelled training voxels increases, the semi-supervised method has less of an advantage over the supervised method. Bai et al. [2017] experiment with two numbers of scans used for the training set, and find that the increase in performance of the semi-supervised method is less prominent when more labeled data is available. Gu et al. [2017] show learning curves where performance of both supervised and semi-supervised methods increases with the number of samples, and that the gap between the two methods decreases.

C. Graph-based methods and regularization

Another popular strategy is to use the unlabeled data to better estimate the distribution of the data, and as such, regularize the classifier. Graph-based methods and semi-supervised SVMs fall under this category, but make different assumptions about the data.

Graph-based methods construct a graph with the samples as nodes, and similarities of these samples (defined via the Euclidean distance and/or prior knowledge) as edges. The assumption is that connected samples are likely to have the same label, and the goal is to propagate the labels along the graph. This can be achieved by with a graph cut algorithm, which finds a labeling of the samples such that the outputs for the labeled training samples are correct, and the outputs of all samples are smooth along the graph. In the surveyed papers, graph cuts are often used for segmentation [Mahapatra et al., 2016, Song et al., 2009, Ciurte et al., 2014, Wang et al., 2014, Su et al., 2016], the labels are therefore propagated between pixels or superpixels. However, finding a labeling means that previously unseen images cannot be labeled without running the procedure again.

Graph-based methods can be also used for atlas-based segmentation [Gass et al., 2012, Borga et al., 2016], but with an important difference. Instead of constructing a graph of pixels, atlas-based segmentation methods construct a graph of images. When segmenting a test image, the labels of a single atlas are first propagated to the (unlabeled) images that are neighbors on this graph. These atlases with propagated labels can then be combined into a final labeling.

Manifold regularization uses a similar idea of smoothness along a graph, and is able to label previously unseen data. Here the graph Laplacian (which encodes the similarity of the nodes) is used as a regularizer which encourages smoothness along the graph. This method is used both for segmentation [Song et al., 2009, Park et al., 2014] and computer-aided diagnosis [Iwari et al., 2010, An et al., 2016, Batmanghelich et al., 2011, Wang et al., 2017].
to fitting a hyperplane using the labeled training samples, semi-supervised SVMs also try to enforce this assumption, by favoring hyperplanes which place unlabeled samples outside the margin. This approach is used for classification of AD or MCI \cite{Filipovych2011,Moradi2015}.

A sample is a bag or set \( X_i = \{ x_{ij} | j = 1, ..., N_i \} \subset \mathbb{R}^m \) of \( N_i \) instances, each instance is thus a \( m \)-dimensional feature vector. We are given labeled training bags \( \{(X_i, Y_i)|i = 1, ..., N_S\} \) where \( Y_i \in \{0,1\} \). The standard assumption is that there exist hidden instance labels \( y^{\text{hidden}} \in \{0,1\} \) which relate to the bag labels as follows: a bag is positive if and only if it contains at least one positive instance. Over the years, several other assumptions have been proposed \cite{Foulds2010}. A popular assumption is the collective assumption, where all instances (rather than only the most positive one, as in the standard assumption) contribute to the bag label.

IV. MULTIPLE INSTANCE LEARNING

The multiple-instance learning (MIL) scenario can occur when obtaining ground-truth local annotations (i.e. for pixels or patches) is costly and time-consuming, but global labels for whole images, such as the overall condition of the patient, are available more readily. However, these labels do not apply to all the pixels or patches inside the image. MIL is an extension of supervised learning which can train classifiers using such weakly labeled data. For example, a classifier trained on images (bags), where each bag is labeled as healthy or abnormal and consists of unlabeled image patches (instances), would be able to label novel images, and/or patches of that image as healthy or abnormal.

A sample is a bag or set \( X_i = \{ x_{ij} | j = 1, ..., N_i \} \subset \mathbb{R}^m \) of \( N_i \) instances, each instance is thus a \( m \)-dimensional feature vector. We are given labeled training bags \( \{(X_i, Y_i)|i = 1, ..., N_S\} \) where \( Y_i \in \{0,1\} \). The standard assumption is that there exist hidden instance labels \( y^{\text{hidden}} \in \{0,1\} \) which relate to the bag labels as follows: a bag is positive if and only if it contains at least one positive instance. Over the years, several other assumptions have been proposed \cite{Foulds2010}. A popular assumption is the collective assumption, where all instances (rather than only the most positive one, as in the standard assumption) contribute to the bag label.

Originally, the goal in MIL was to train a bag classifier \( f_B \) to label previously unseen bags. Several MIL classifiers do this by inferring an instance classifier \( f_I \), and combining the outputs of the bag’s instances, for example by the noisy-or rule: \( f_B(X_i) = \max_k \{f_i(x_{ij})\} \). Another group, bag-level classifiers, typically represent each bag as a single feature vector and use supervised classifiers for training \( f_B \) directly. Such classifiers are often robust, but usually cannot provide instance labels. Following Quellec et al. \cite{Quellec2017}, we refer to methods which can provide instance labels as “primarily bag level” and methods which cannot as “exclusively bag level”. For an in-depth review of MIL (not limited to medical applications), see Batmanghelich et al. \cite{Batmanghelich2011}.

### TABLE III: Overview of semi-supervised learning applications. The last column describes the type of method used, “active” refers to active learning.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Application</th>
<th>SSL category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Song et al. 2009</td>
<td>tumor segmentation</td>
<td>graph-based</td>
</tr>
<tr>
<td>Iglesias &amp; 2010</td>
<td>skull stripping</td>
<td>self-training</td>
</tr>
<tr>
<td>Filipovych 2011</td>
<td>classification of MCI</td>
<td>semi-supervised SVM</td>
</tr>
<tr>
<td>Brannan et al. 2011</td>
<td>classification of AD, MCI</td>
<td>graph-based</td>
</tr>
<tr>
<td>Xie et al. 2013</td>
<td>tissue segmentation</td>
<td>graph-based</td>
</tr>
<tr>
<td>Meier et al. 2014</td>
<td>tumor segmentation</td>
<td>graph-based</td>
</tr>
<tr>
<td>Dittrich et al. 2014</td>
<td>fetal brain segmentation</td>
<td>self-training</td>
</tr>
<tr>
<td>Wang et al. 2014</td>
<td>lesion segmentation</td>
<td>self-training, active</td>
</tr>
<tr>
<td>Xu et al. 2016</td>
<td>AD classification</td>
<td>graph-based</td>
</tr>
<tr>
<td>Baur et al. 2017</td>
<td>MS lesion segmentation</td>
<td>graph-based</td>
</tr>
<tr>
<td>Moradi et al. 2015</td>
<td>classification of MCI</td>
<td>semi-supervised SVM</td>
</tr>
<tr>
<td>Adal et al. 2014</td>
<td>microaneurysm detection</td>
<td>self-training</td>
</tr>
<tr>
<td>Mahapatra 2016</td>
<td>optic disc missing annotation prediction</td>
<td>self-training, graph-based</td>
</tr>
<tr>
<td>Sun et al. 2016</td>
<td>mass classification</td>
<td>co-training</td>
</tr>
<tr>
<td>Zuluaga et al. 2011</td>
<td>detection of vascular lesions</td>
<td>self-training</td>
</tr>
<tr>
<td>Bai et al. 2017</td>
<td>cardiac segmentation</td>
<td>self-training</td>
</tr>
<tr>
<td>Wang et al. 2017</td>
<td>aneurysm volume estimation</td>
<td>graph-based</td>
</tr>
<tr>
<td>Prasad et al. 2009</td>
<td>segmentation of emphysema in CT</td>
<td>self-training / co-training, active</td>
</tr>
<tr>
<td>van Rikxoort et al. 2010</td>
<td>classification of tuberculosis patterns in CT</td>
<td>self-training / co-training, active</td>
</tr>
<tr>
<td>Tywart et al. 2010</td>
<td>classification of cancerous areas in prostate</td>
<td>graph-based</td>
</tr>
<tr>
<td>Park et al. 2014</td>
<td>prostate segmentation</td>
<td>graph-based, active</td>
</tr>
<tr>
<td>Borga et al. 2016</td>
<td>liver segmentation</td>
<td>graph-based</td>
</tr>
<tr>
<td>Mahapatra 2016</td>
<td>predicting missing expert annotations of Crohn’s disease</td>
<td>self-training, graph-based</td>
</tr>
<tr>
<td>Singh et al. 2011</td>
<td>cell type classification in microscopy</td>
<td>self-training</td>
</tr>
<tr>
<td>Parag et al. 2014</td>
<td>cell type segmentation in microscopy</td>
<td>graph-based, active</td>
</tr>
<tr>
<td>Su et al. 2016</td>
<td>cell segmentation in microscopy</td>
<td>graph-based</td>
</tr>
<tr>
<td>Gass et al. 2012</td>
<td>segmentation in two applications</td>
<td>graph-based</td>
</tr>
<tr>
<td>Ciurte et al. 2014</td>
<td>segmentation in four applications</td>
<td>graph-based</td>
</tr>
<tr>
<td>Gu et al. 2017</td>
<td>segmentation in two applications</td>
<td>self-training</td>
</tr>
<tr>
<td>Huang et al. 2008</td>
<td>segmentation of nasopharyngeal carcinoma in MR</td>
<td>graph-based</td>
</tr>
</tbody>
</table>

Brain

Table: Overview of semi-supervised learning applications. The last column describes the type of method used, “active” refers to active learning.
Because instance-level and some bag-level classifiers can provide instance labels, the focus of MIL became two-fold: classifying bags and classifying instances. This distinction also exists in medical imaging, as discussed in the next section.

A. MIL in medical imaging

MIL is a natural learning scenario for medical image analysis because labels are often not available at the desired granularity. The goal is therefore to exploit weaker bag labels for training. This idea can be used for different types of tasks. We adopt a categorization similar to that of [Quellec et al., 2017]: global detection, i.e. classifying the image as having a target pattern, local detection, i.e. classifying an image patch as having a target pattern and false positive reduction (classifying an candidate lesion as true or false positive). Quellec et al. [2017] also discuss a “miscellaneous categorization” category, however, we find that this is very similar to “global detection”.

The contributions are summarized in Table IV. The most common scenario where MIL is used, is global detection - classifying an entire image as having a particular disease or not. We discuss this in Section IV-B. However, instance classification - local detection - is also relevant, as we would like to know where the abnormalities are present. These goals are sometimes pursued simultaneously (Section IV-C). If only global detection addressed, often local detection is relevant, but could not be addressed due to lack of labeled instances. In a few cases, only local detection is addressed (Section IV-D).

Another application of MIL is false positive reduction classifying candidate lesions or tumors, which may have been extracted by other algorithms. In this context, the candidate is the bag, and a different viewpoint (different patch, viewpoint or frame of video) of the candidate is an instance. In other words, the instance has an “is a” relationship to the bag, and the instances can be highly correlated, and no instances are truly negative. Here the goal is to classify the bag, and there is no logical instance classification task. We discuss this task in Section IV-E.

B. Global detection

The majority of papers on MIL address global detection. The use of MIL is motivated by the fact that strong labels which would enable using supervised learning for local (and therefore also global) detection are not available. Weak labels are available more readily, but may not apply to the entire scan.

This task is applicable to many different applications, the more common ones being detection of diabetic retinopathy in retinal images [Venkatesan et al., 2012, Quellec et al., 2012, Kandemir and Hamprecht, 2015] and detection of cancerous regions in histopathology images [Kandemir and Hamprecht, 2015, Xu et al., 2014, Li et al., 2015]. Although weak labels are available more easily, the datasets can still be quite small, starting at just 58 bags in a dataset of breast cancer in microarray images [Kandemir and Hamprecht, 2015]. Others, such as datasets of COPD in chest CT images [Cheplygina et al., 2014] or tuberculosis in chest x-ray [Melendez et al., 2014, 2016] are in the order of a thousand scans. Only recently, very large datasets started appearing, such as the dataset of 100K chest x-rays used in [Li et al., 2017b].

Global detection can be achieved both with instance-level methods and bag-level methods. Overall, bag-level methods seem to be more successful due to their ability to not treat instances independently (as instance-level methods would), but instead consider the correlations and structure of the instances. In such cases a MIL method can even outperform a fully supervised method [Kandemir and Hamprecht, 2015, Wang et al., 2015a, Vural et al., 2006, Samsudin and Bradley, 2010], showing that the lack of strong labels is not the only use case for MIL.

In some cases, these scenarios where it is best not to consider instances independently, are not referred to as MIL, but “batch classification” [Vural et al., 2006] or “group-based classification” [Samsudin and Bradley, 2010]. An overview of these scenarios and their relationships to MIL can be found in [Cheplygina et al., 2015b].

C. Global and local detection

Several papers focus both on global and local detection. For example in detection of tuberculosis [Melendez et al., 2014, 2016] it is important to both classify the image as having tuberculosis, and highlight the tuberculosis lesions in the image. In fact, in all papers where global detection is the focus, a local detection task could be defined. However, these local detection tasks are often not addressed, since no labels are available for validation, for example [Cheplygina et al., 2015a, Kandemir and Hamprecht, 2015].

When both tasks can be addressed, this is done with either instance-level or primarily bag-level methods, which can provide instance labels. However, solving two tasks with a single classifier introduces a problem, often overlooked in literature - that the best bag classifier is not necessarily the best instance classifier and vice versa. Cheplygina et al. [2015a] propose an unsupervised measure of instance level quality and demonstrates that the best bag classifier can lead to unstable instance predictions, when trained on bootstrapped versions of the training set. Kandemir and Hamprecht [2015] compare several classifiers on a dataset of Barrett’s cancer diagnosis in histopathology image, for which both bag-level and instance-level labels are available. The best bag classifier is miGraph which is an exclusively bag-level method, while the best instance classifier is miSVM, which performs reasonably well on bags, but does not have the highest performance.

Papers where both global and local labels are available for training, show similar results. Li et al. [2017b] use both a large amount of bag labels and a smaller amount of instance labels to train a classifier for global adn local detection of various chest x-ray abnormalities. The results show that, when instance classification is the goal, adding more labelled bags does not necessarily increase instance-level performance. Shin et al. [2017] use both bag and instance labels for localization and classification of breast masses. They show that bag labels should be given less weight than the instance labels - i.e. using all the labels together does not lead to the best results.
### TABLE IV: Overview of multiple instance learning applications. The third column refers to the type of problem addressed - global and or local detection or false positive reduction. The fourth column refers to the type of classifier used - exclusively (excl bag) or primarily (prim bag) bag-level, or instance-level.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Application</th>
<th>MIL category</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tong et al. [2014]</td>
<td>AD classification</td>
<td>global</td>
<td>excl bag</td>
</tr>
<tr>
<td>Chen et al. [2015b]</td>
<td>cerebral small vessel disease detection</td>
<td>global</td>
<td>instance</td>
</tr>
<tr>
<td>Dubost et al. [2017]</td>
<td>enlarged perivascular space detection</td>
<td>local</td>
<td>instance</td>
</tr>
<tr>
<td><strong>Eye</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venkatesan et al. [2012]</td>
<td>diabetic retinopathy classification</td>
<td>global</td>
<td>excl bag</td>
</tr>
<tr>
<td>Quellec et al. [2012]</td>
<td>diabetic retinopathy classification</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td>Schlegl et al. [2015]</td>
<td>fluid segmentation</td>
<td>local</td>
<td>instance</td>
</tr>
<tr>
<td>Manivannan et al.</td>
<td>retinal nerve fiber layer visibility classification</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td>Li et al. [2017]</td>
<td>fluid detection</td>
<td>global</td>
<td>instance</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maken et al. [2014]</td>
<td>breast cancer detection</td>
<td>global</td>
<td>multiple</td>
</tr>
<tr>
<td>Sanchez de la Rosa et al. [2015]</td>
<td>breast cancer detection</td>
<td>global, local</td>
<td>excl bag</td>
</tr>
<tr>
<td>Shin et al. [2017]</td>
<td>mass localization, classification</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dundar et al. [2007]</td>
<td>pulmonary embolism detection</td>
<td>false positive</td>
<td>instance</td>
</tr>
<tr>
<td>Li et al. [2017]</td>
<td>pulmonary embolism detection</td>
<td>false positive</td>
<td>instance</td>
</tr>
<tr>
<td>Liang and Bi [2007]</td>
<td>COPD classification</td>
<td>global</td>
<td>multiple</td>
</tr>
<tr>
<td>Cheplygina et al. [2014]</td>
<td>tuberculosis detection</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td>Meltendez et al. [2014]</td>
<td>lung cancer lesion classification</td>
<td>false positive</td>
<td>instance</td>
</tr>
<tr>
<td>Stantavas et al. [2014]</td>
<td>tuberculosis detection</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td>Meltendez et al. [2016]</td>
<td>tuberculosis detection</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td>Kim and Hwang [2016]</td>
<td>lung cancer malignancy prediction</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td>Shen et al. [2016]</td>
<td>COPD classification</td>
<td>global</td>
<td>instance</td>
</tr>
<tr>
<td>Cheplygina et al. [2017]</td>
<td>abnormality detection (14 classes)</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td>Li et al. [2017b]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abdomen</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dundar et al. [2007]</td>
<td>polyp detection</td>
<td>false positive</td>
<td>instance</td>
</tr>
<tr>
<td>Wu et al. [2009]</td>
<td>polyp detection</td>
<td>false positive</td>
<td>instance</td>
</tr>
<tr>
<td>Li et al. [2012]</td>
<td>polyp detection, size estimation</td>
<td>false positive</td>
<td>instance</td>
</tr>
<tr>
<td>Wang et al. [2012]</td>
<td>lesion detection</td>
<td>global</td>
<td>prim bag</td>
</tr>
<tr>
<td>Wang et al. [2015a]</td>
<td>lesion detection</td>
<td>global</td>
<td>prim bag</td>
</tr>
<tr>
<td>Wang et al. [2015b]</td>
<td>lesion detection</td>
<td>global</td>
<td>prim bag</td>
</tr>
<tr>
<td><strong>Histology/Microscopy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dundar et al. [2010]</td>
<td>breast lesion detection</td>
<td>global</td>
<td>instance</td>
</tr>
<tr>
<td>Satisham and Bradley [2010]</td>
<td>pap smear classification</td>
<td>global, multiple</td>
<td></td>
</tr>
<tr>
<td>McCann et al. [2015]</td>
<td>skin biopsy annotation</td>
<td>global</td>
<td>multiple</td>
</tr>
<tr>
<td>Zhang et al. [2015]</td>
<td>breast cancer detection</td>
<td>global</td>
<td>excl bag</td>
</tr>
<tr>
<td>Kandemir et al. [2014]</td>
<td>colon cancer detection</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td>Ali et al. [2014]</td>
<td>glioblastoma, low-grade glioma detection</td>
<td>global</td>
<td>instance</td>
</tr>
<tr>
<td>Hou et al. [2015]</td>
<td>breast cancer detection</td>
<td>global</td>
<td>prim bag</td>
</tr>
<tr>
<td>Mercan et al. [2016]</td>
<td>breast cancer detection</td>
<td>global</td>
<td>instance</td>
</tr>
<tr>
<td>Jia et al. [2017]</td>
<td>cancerous region segmentation (colon)</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td>Tomeczak et al. [2017]</td>
<td>breast cancer detection</td>
<td>global</td>
<td>instance</td>
</tr>
<tr>
<td><strong>Multiple</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vural et al. [2006]</td>
<td>abnormality detection in three applications</td>
<td>false positive</td>
<td>instance</td>
</tr>
<tr>
<td>Kandemir and Hamprecht [2015]</td>
<td>abnormality detection in two applications</td>
<td>global, multiple</td>
<td></td>
</tr>
<tr>
<td>Hwang and Kim [2016]</td>
<td>lesion detection in two applications</td>
<td>global, local</td>
<td>instance</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Situ et al. [2010]</td>
<td>dermoscopic feature annotation</td>
<td>global</td>
<td>prim bag</td>
</tr>
<tr>
<td>Liu et al. [2010]</td>
<td>cardiac event detection</td>
<td>global</td>
<td>instance</td>
</tr>
<tr>
<td>Yan et al. [2016]</td>
<td>bodypart recognition</td>
<td>global</td>
<td>instance</td>
</tr>
</tbody>
</table>

**D. Local detection only**

More recently methods which focus only on the local detection task. These methods usually refer to themselves as weakly supervised - a term sometimes interchangeably used with MIL. In some cases, the weak supervision refers to learning from bag labels, which is when the MIL scenario is relevant. For example, Dubost et al. [2017] address detection of enlarged perivascular spaces in brain MR images, by training only on lesion counts (weak labels) for the images. However, estimating lesion counts for test images is done only as a step before lesion localization - it is not a task on its own, that is evaluated in the experimental results.

The terms MIL and weak supervision are not always interchangeable. Donner et al. [2009] address the segmentation of anatomical structures with a sparse appearance model. Only one annotation is needed, and label propagation is used in the process. We would classify this approach as semi-supervised. Rajchl et al. [2016] address weak supervision for fetal brain segmentation. Weak here is referring the superpixel labels being approximately correct.
E. False positive reduction

A task that also focuses on classification of bags, but uses different assumptions, is false positive reduction. Here the bag represents a candidate tumor or lesion (possibly detected by a different method), and the instances represent different viewpoints [Wu et al., 2009; Lu et al., 2011; Wang et al., 2012]. The bag label in principle applies to all the instances, since they are versions of the same candidate, which is different from the other MIL scenarios with label ambiguity. However, similar to global detection, a MIL classifier can outperform a supervised classifier, because it benefits from combining information of different instances, to classify the bag.

A difference from global detection is that there is not always a logical instance classification task. The goal is to classify the candidate as a true or false positive, and it is less relevant which viewpoint most influenced this decision.

V. TRANSFER LEARNING

Another, recently very popular learning scenario is transfer learning [Pan and Yang, 2010]. Here the goal is to learn from related learning problems. One example of related learning problems is when the data originates from different distributions. This scenario is common in medical imaging due to heterogeneous diseases or patient groups, and/or due to differences between acquisition of images, such as the use of different scanners or scanning protocols. Another example is related classification tasks for the same data, such as detection of different types of abnormalities.

More formally, the differences can be caused by different marginal distributions $p(x)$, different labeling functions $p(y|x)$, or even different feature and label spaces. In our illustrative example, the X’s are the feature vectors describing the appearance of lung ROIs, and the Y’s are the categories the subjects belong to. Changes in subject groups, scanners and scanning protocols, can affect the distributions $p(x)$, such as “this dataset has lower intensities”, $p(y)$, such as “this dataset has a large proportion of emphysema” and/or $p(y|x)$, such as “in this dataset this appearance corresponds to a different category”.

Based on which characteristics are the same, and which characteristics are different, we can distinguish different types of transfer learning scenarios [Pan and Yang, 2010]. In the inductive transfer learning setting, the goal is to train a classifier for the target task, but the source task is different from the target task. In the transductive transfer learning setting, the source and target tasks are the same, but the source and target domains are different. The third scenario addressed in the survey is unsupervised transfer learning, which is similar to inductive transfer, but the target task is unsupervised, such as clustering.

Transfer learning approaches addressing these scenarios can be grouped by what they transfer: instance transfer i.e. assuming that source data can be reweighted to train the target classifier, feature transfer i.e. encoding knowledge from the source domain into the feature representation, parameter transfer, i.e. encoding the knowledge into parameters or priors, and relational knowledge transfer, i.e. assuming that the data in source and target domains have similar structure.

A. TL in medical imaging

The contributions are summarized in Table V. We discuss these methods based on whether the tasks and the domains are the same or different.

In the same domain, different task scenario (Section V-B), we are often dealing with multiple tasks for the same set of images, such as detecting multiple types of abnormalities, where detection of each type of abnormality is a binary classification problem. This is often approached with feature transfer - learning features which are relevant for multiple tasks, thus effectively increasing the sample size and/or regularizing the classifier. An in-depth explanation of why this works can be found in Ruder [2017]. Rather than training multiple tasks simultaneously, representation learning approaches where an (unsupervised) task such as reconstructing the data, is done first, are also possible.

In the “different domain, same task” scenario (Section V-C), we are dealing with, for example, data acquired with different scanners. This is often addressed with instance transfer. Instance transfer involves, for example, weighting source training samples such that only relevant samples receive high weights, or realigning the source domain with the target domain, and thus using the additional aligned instances for training. These approaches are aimed at decreasing the number of irrelevant samples, and/or increasing the number of relevant samples.

Finally, there is also a different task, different domain scenario (Section V-D). Although according to Pan and Yang [2010] this would fall under “unsupervised transfer learning” and only address clustering, we find that this is also relevant in the supervised case, through feature transfer. In this case, the source task is used to pretrain a network. The network can then be used in two strategies [Litjens et al., 2017]: for feature extraction, or as a starting point for further training (fine-tuning) of the target task. Both are currently very popular in medical image analysis.

B. Same domain, different tasks

Perhaps the earliest way in which transfer of information was leveraged within medical imaging, is inductive transfer learning, or learning different tasks within the same domain. For example, in lung images, we might be interested in detecting different types of abnormalities. The intuition is that these tasks will share task-independent features, and learning these tasks jointly increases the amount of data, leading to a more robust representation. According to Pan and Yang this scenario includes multi-task learning (MTL), where a lot labeled source data is available, and self-taught learning, where no labeled source data is available.

We find that in medical imaging, many works fall under the multi-task learning scenario. Bi et al. [2008] describe a probabilistic framework for MTL algorithms and apply it to two applications with different characteristics. The first application is classifying nodules in chest CT, while also using labeled examples of ground glass opacities. This increases the effective sample size, even though the tasks are different. The second application is classifying multiple heart wall segments
<table>
<thead>
<tr>
<th>Reference</th>
<th>Topic</th>
<th>Task</th>
<th>Domain</th>
<th>Transfer type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Huang et al. [2017]</strong></td>
<td>epithelium stroma</td>
<td>classification</td>
<td>same</td>
<td>different feature, pretraining</td>
</tr>
<tr>
<td><strong>Murthy et al. [2016]</strong></td>
<td>tumor segmentation</td>
<td>classification</td>
<td>different</td>
<td>instance, weight</td>
</tr>
<tr>
<td><strong>Chang et al. [2017]</strong></td>
<td>tissue classification</td>
<td>classification</td>
<td>different</td>
<td>instance, weight</td>
</tr>
<tr>
<td><strong>Gadermayr et al. [2016]</strong></td>
<td>AD classification</td>
<td>classification</td>
<td>same</td>
<td>instance, weight</td>
</tr>
<tr>
<td><strong>Menegola et al. [2017]</strong></td>
<td>melanoma classification</td>
<td>classification</td>
<td>different</td>
<td>different feature, pretraining</td>
</tr>
<tr>
<td><strong>Liu et al. [2017]</strong></td>
<td>thyroid nodule</td>
<td>classification</td>
<td>different</td>
<td>different feature, pretraining</td>
</tr>
<tr>
<td><strong>Murphree and Ngufor [2017]</strong></td>
<td>melanoma classification</td>
<td>classification</td>
<td>different</td>
<td>different feature, pretraining</td>
</tr>
<tr>
<td><strong>Conjeti et al. [2016]</strong></td>
<td>tissue classification</td>
<td>classification</td>
<td>different</td>
<td>instance, align</td>
</tr>
<tr>
<td><strong>Antony et al. [2016]</strong></td>
<td>osteoarthritis</td>
<td>localization</td>
<td>different</td>
<td>feature, multi-task</td>
</tr>
<tr>
<td><strong>Cooper et al. [2016]</strong></td>
<td>skin lesion classification</td>
<td>classification</td>
<td>different</td>
<td>instance, align</td>
</tr>
<tr>
<td><strong>Munirude and Ngure [2017]</strong></td>
<td>melanoma classification</td>
<td>classification</td>
<td>different</td>
<td>feature, pretraining</td>
</tr>
<tr>
<td><strong>Liu et al. [2017]</strong></td>
<td>thyroid nodule</td>
<td>classification</td>
<td>different</td>
<td>different feature, pretraining</td>
</tr>
<tr>
<td><strong>Menegola et al. [2017]</strong></td>
<td>melanoma classification</td>
<td>classification</td>
<td>different</td>
<td>different feature, pretraining</td>
</tr>
</tbody>
</table>
| **TABLE V: Overview of transfer learning applications. The last column refers to the type of transfer approach, i.e. whether it is instance transfer (by weighting or aligning samples) or feature transfer (by pretraining on an auxiliary task in the same or different domain, or multi-task learning)**
per subject. Instead of classifying each segment independently, they simultaneously classify all segments, essentially predicting a vector of labels per subject. This does not increase the sample size, but regularizes the classifier. The authors also demonstrate that MTL has most advantage at low sample sizes, where regularization is most needed.

Multi-task learning is also used in classification of Alzheimer’s disease in brain MR images. Usually subjects are classified into AD, MCI and cognitively normal (CN) classes. Additionally, MCI subjects can be classified into converters (to AD) and non-converters. Here again there are two main strategies. Effective increase of the sample size can be seen in [Cheng et al., 2015] for MCI conversion prediction.

Using multiple labels can be seen in [Zhang and Shen, 2012]. Motivated by the fact that the underlying pathology influences both the diagnosis (Alzheimer’s, mild cognitive impairment or cognitively normal) and two cognitive scores, they predict these three labels simultaneously. In a further experiment, they predict the change in these labels, i.e. the absolute change in the cognitive scores, and whether the MCI subjects convert to AD or not.

Other applications where multiple labels are predicted include classification of lung diseases [Li et al., 2017b], and classification of visual attributes of images, such as attributes of lung nodules [Chen et al., 2017b] or skin lesions [Murthy et al., 2017].

Finally, there are a couple of examples of self-taught learning, where there are labels for only one of the tasks. This happens in scenarios where one dataset needs to address multiple tasks, for example localization of abnormalities and their classification [Hwang and Kim, 2016], or description [Kisilev et al., 2016]. There are then two optimization problems being solved, but using the same labels. Note that while Pan and Yang call these works “self-taught learning”, in practice other names may be used, such as “self-transfer learning” [Hwang and Kim, 2016] or multi-task learning [Kisilev et al., 2016].

In the examples above, multi-task learning is done by sharing the weights or parameters for the model, but using different outputs depending on the task. For example, in deep learning, this could be achieved by sharing the hidden layers, but using a different set of output layers. The label space for each of the tasks is therefore the same, as if that task was learnt individually. An exception is [Moeskops et al., 2016], where multiple tasks are learnt in a joint label space. While in principle this means that confusion between tasks could occur, the results show that most errors happen within the same task. Another way to use different tasks within the same domain, is by learning the tasks sequentially, rather than in parallel, as in multi-task learning. For example, Dhungel et al. [2017] first train a regression model to predict handcrafted features that are known to be related to the target labels. This model is then used for initialization of the target model. Although the handcrafted features are used as labels, they are not provided by experts, so this type of pretraining can be considered to be unsupervised.

There are other ways to add such unsupervised tasks to improve the target (supervised) task. An approach that is gaining popularity is finding a representation from which (part of) the data can be reconstructed. For example, [Ross et al., 2017] first decolorize their training images, then use recolorization as an additional task to learn a good representation.

C. Different domains, same task

Other early efforts in transfer learning in medical imaging focus on the transductive transfer learning scenario, where the classification task is the same, but the domains are different, for example due to the use of data from different hospitals. Due to the differences in data distributions, it may not be optimal to simply train a classifier on one domain, and then test it on the other domain, or to train a classifier on the union of all available labeled data.

Changes in distributions can occur due to several reasons. For example, van Opbroek et al. [2015b] address segmentation of MR data from different scanners, which alters the appearance of the images, and different populations, which changes the distribution of classes in the data. Conjeti et al. [2016] address differences between in vitro and in vivo ultrasound, where the absence/presence of blood flow causes a distribution shift. Bermúdez-Chacón et al. [2016] focus on segmentation of cells in microscopy images of different parts of the brain, which results in heterogeneous appearances.

The methods which address these distributions are mainly instance-transfer methods. One strategy is to change the source distribution by weighting the instances for training, such that the source distribution matches the target distribution as closely as possible. This is possible via importance weighting, where each instance is assigned a weight based on probability of belonging to the target domain. This strategy is optimal if only the marginal distributions are different but the labeling functions are the same, but in practice can also be helpful with different labeling functions [van Opbroek et al., 2015b, Cheplygina et al., 2017]. Weights can also be assigned on other characteristics, without explicitly addressing the distributions of the feature vectors. When classifying subjects as having Alzheimer’s, Wachinger and Reuter [2016] perform weighting based on patient characteristics such as age, while these factors are not used by the classifier.

Another instance-transfer strategy is to align the source and target domains by a transformation of the feature space. Once the domains are aligned, the instances of the source domain can be used for training. Conjeti et al. [2016] use principal component analysis to align in vitro and in vivo ultrasound images as a preprocessing step, before training a random forest on the source data and adapting it with the (aligned) target data. Guerrero et al. [2014] align MR scans from different hospitals. According to [Pan and Yang, 2010], in transductive transfer learning there is no labeled data from the target domain. However in practice, these methods differ in whether they use labeled data from the target domain. Unsupervised transfer in addressed in [Wang et al., 2013], [Heimann et al., 2014, Cheplygina et al., 2017]. Other works focus on supervised...
transfer, with a small amount of labeled data from the target domain [Conjeti et al., 2016] [Wachinger and Reuter, 2016] [Goetz et al., 2016].

D. Different task, different domains

With the developments of deep learning methods, it has become more common to transfer information between different tasks and different domains. The survey of Pan and Yang [2010], published before such methods were popular does not fully account for this situation. While a “different task, different domain” scenario is described, it is said only to “focus on solving unsupervised learning tasks in the target domain”, which is not the case for the works described below.

The authors find that images which are in a sense similar to melanoma images, Diabetic Retinopathy (KaggleDR) and use two datasets for pretraining: Imagenet and Kaggle finetuning strategies for the task of melanoma classification, while varying other parameters of the classifier. This indeed leads to higher recognition rates, also polyps. This is expected due large homogeneous areas present in brain CT, but not in lung CT, which has more texture information.

The source data can be from a totally different task. Using non-medical images as source data is now common. Probably the first work to do this is Schlegl et al., 2014. For the target task of classifying tissue types in chest CT slices, they used three different source tasks: natural images, other chest CT images, and head CT images. They found that natural images performed comparably or even slightly better than using only lung images. Using brain images was less effective, possibly due large homogeneous areas present in brain CT, but not in lung CT, which has more texture information.

Now transfer from natural images is quite popular, such as datasets annually released by the Imagenet Large Scale Visual Recognition Challenge [Russakovsky et al., 2015]. The datasets have more than a million images and thousand categories of everyday objects. Since this methodology is so popular, we are not able to provide an exhaustive list of papers which apply it, and focus on papers which investigate underlying causes of when transfer is successful or not.

For detecting and classifying colorectal polyps, Zhang et al., 2017 transfer from Imagenet and from Places, a large scene recognition dataset with categories such as “basement” or “bathroom” [Zhou et al., 2017]. Zhang et al., 2017 hypothesize that Places has higher similarity between classes than Imagenet, which would help distinguish small differences in polyps. This indeed leads to higher recognition rates, also while varying other parameters of the classifier.

Menegola et al., 2017 compare off-the-shelf features and finetuning strategies for the task of melanoma classification, and use two datasets for pretraining: Imagenet and Kaggle Diabetic Retinopathy (KaggleDR) [KaggleDR contains retinal images which are in a sense similar to melanoma images, capturing a single object of interest. The authors find that finetuning outperforms the off-the-shelf strategy, and that transfer from Imagenet only is more successful than transfer from KaggleDR, or from the union of the datasets. Ribeiro et al., 2017 investigate pretraining and fine-tuning of different source datasets for classification of polyps in endoscopy images. They find that texture datasets perform best as source data, but if the size of the source dataset is small, it is better to select a larger unrelated source dataset.

These results do not always hold. In a study of predicting response to cancer treatment in the bladder, Cha et al., 2017 compare networks without TL, pretrained on natural images, and pretrained on bladder ROIs. They find that there are no statistically significant differences between the methods.

Despite the popularity of this approach, it was not always apparent that this was possible. For example, Hwang and Kim, 2016 state that it’s not possible to pretrain a network for medical data, because the data is not similar. However, the results summarized in this section suggest that diversity of source data might be more important than its similarity to the target.

VI. DISCUSSION

A. Trends

We first examine the overall trends in the use of different learning scenarios. Fig. 2 shows how the papers for each scenario are distributed across different years. Transfer learning is clearly the most popular, although this has only become evident in recent years. A reason for this might be the availability of datasets and tools. For semi-supervised and multiple instance learning, a specific type of data/labels need to be available, while for transfer learning, it is possible to use a completely external dataset in addition to the target data.

There are also trends related to the different application areas. In this paper we have used the following categories, as inspired by Litjens et al., 2017: brain, retina, chest, breast, heart, abdomen, histology/microscopy and other applications. Fig. 3 shows the distribution of these applications across the learning scenarios. Overall, brain is the most popular application, followed by histology/microscopy and the abdomen. Breast, heart and retina, on the other hand, have relatively few papers. Around 10% of the papers address multiple applications.
The application also influences the popularity of different learning scenarios. For example, MIL is frequently used for histology/microscopy, but is not as common for tasks within the brain. One reason for these differences could be the suitability of the available data for the learning scenario. For example, in histology it is reasonable to assume that the patches within an image do not have an ordering, and there can be a variable number of patches per image, as is the case in multiple instance learning. However, this is less suitable for the brain, where anatomical correspondences are informative, and the MIL scenario is less applicable.

B. Related learning scenarios

There are several links between MIL and TL. Using MIL can avoid the need to use a TL method, because MIL labels from the same domain can be acquired more easily. This is illustrated in [Melendez et al., 2014], where instance labels are available only for one domain, but bag labels are available for multiple domains. A MIL classifier trained on same-domain bag labels outperforms a fully supervised classifier trained on different-domain instance labels. It would have been valuable to see how a TL approach would compare to the same-domain MIL method, and to the combination of both.

Another link between MIL and TL is in scenarios where two related classification tasks are addressed, such as global detection and local detection. In TL methods this is usually achieved by training a single classifier, but we can also view this as an example of multi-task or self-transfer learning, where two classifiers are trained with a shared representation. Finally, we could consider situations where there is no distribution shift on instance level, but only on bag level, and vice versa.

There are also opportunities in exploring learning scenarios which are not as popular in medical imaging. Positive and unlabeled learning [Elkan and Noto, 2008] has received quite some attention in the machine learning community. The idea is to learn from only positive and unlabeled examples, which may happen when during annotation, the expert can miss other positives. The absence of a positive label does not imply that an example is negative, and thus a non-positive example is considered unlabeled. Although this scenario seems very suitable for medical imaging, the only paper we have found directly addressing this scenario is [Zuluaga et al., 2011].

Other possibilities include the “siblings” of MIL, such as batch classification [Vural et al., 2006] and group-based learning [Samsudin and Bradley, 2010]. We have grouped these works in the MIL section, as they can be seen as variations of MIL with different assumptions [Cheplygina et al., 2015b]. Although from the point of literature search it is counterproductive to use such different names for these scenarios, their similarities and differences could help us better understand the diversity of MIL problems being addressed in the literature.

C. Full potential of available data

The available (labeled) data is not always used to its full potential, possibly due to the constraints of a particular method. For example, papers on MIL may convert a regression or multi-class problem into a binary problem. As a result, different grades or types of a disease can be aggregated into “healthy” and “abnormal”. Others may remove more difficult classes. However, this is not necessary helpful for machine learning methods. For example, [Menegola et al., 2016] demonstrate that removing one of the two disease classes results in lower performance, possibly because the method has less samples in total to learn from.

An opportunity is to use multiple labels when the ground truth is determined by consensus of different experts. Usually the individual labels of the experts are combined into consensus labels, which are then used for training. However, as [Quan et al., 2017] point out, modeling the individual labelers during training outperforms averaging the labelers in advance.
Another opportunity is the use of clinical variables. These are currently not used very often, but can improve prediction \cite{Zhou2013}. Even age or sex could be included as additional labels to predict. While not interesting prediction tasks by themselves, these could be leveraged via multi-task learning, for example, by using these as auxiliary tasks or “hints” \cite{Ruder2017}. Clinical reports with more detailed information, such as describing the location of abnormalities, can also provide additional information \cite{Schlegl2015}.

Finally, the data itself can be used for pretraining in an unsupervised manner, for example by reconstructing the data while learning a good representation. This is already being done by a few papers discussed in Section V-B. However, this approach could be an opportunity for other applications where additional images and/or modalities are available, and which could be used as auxiliary tasks.

D. Acquiring additional labels

While the methods in this survey can certainly improve the robustness of classifiers, we feel there is a limit on what can be achieved without additional labels. Active learning methods such as \cite{Melendez2016, Su2016} aim to minimize the number of labels needed for the same or better performance, by only querying the labels that are most ambiguous or will lead to most improvement for the classifier. Given the same budget for labels, this could potentially lead to better performance overall.

Following the success of crowdsourcing in computer vision, crowdsourcing is also gaining an important place in medical imaging. These methods aim to collect (possibly noisy) labels from the public. When combining multiple annotators, the noise is expected to be reduced. Most studies to date investigated the quality of such labels compared to expert labels \cite{Maier-Hein2015, Cheplygina2016, Mitry2015}. Methods which use the crowdsourced labels inside machine learning methods, are less common, for example \cite{Albarqouni2016}. We expect that this will be an important direction for future research.

E. Generalization

A main challenge with not-so-supervised learning in medical imaging is that most works are proofs of concept on one or (less frequently) few applications. This makes it difficult to generalize the results and gain insight into whether the method would work in a different problem.

One partial solution would be to vary the characteristics of a single dataset - for example, subsample the training data to create learning curves, change the class priors to investigate the influence of class imbalance, or select or merge different classes. Another partial solution would be to perform ablation experiments, i.e. removing a part of the method’s functionality, to understand what factors contribute most to the result.

A related challenge of not generalizing to other applications is publication bias: negative results, and/or results from an existing method may not be published, or published in a less popular venue. Borji \cite{Borji2018} provides an excellent discussion on why this is detrimental to research in computer vision. We feel that this is something that should also be discussed within the medical imaging community.

Challenges such as grand-challenges.org are a great resource for benchmarking algorithms on open datasets. However, these too often address only a single application, with the risk of overfitting to these datasets as a community. We see a promising research direction in platforms where the same methods could be applied to a range of datasets from different medical applications.

VII. Conclusion

We have discussed over 140 papers in medical image analysis which focus on classification in a “not-so-supervised” learning scenario, often due to lack of representative annotated data. We focused on semi-supervised, multi-instance and transfer learning, of which transfer learning is the most popular in recent years. While individual papers demonstrate the usefulness of such approaches, there are still many questions on how to best use these methods. We expect future research to benefit from examining the connections between learning scenarios and generalizing the results between applications.

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