A Survey on Tumour Hypoxia from Multi-modal Microscopy Images

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ABSTRACT

Malignant tumors that contain a high proportion of regions privileged of adequate oxygen supply in areas supplied by a microvessel. Given the importance of the estimation of this proportion for improving the clinical prognosis of such treatments, a manual annotation has been proposed, which uses two image modalities of the same histological specimen and produces the number and proportion of MCSUs classified as normoxia (normal oxygenation level), chronic hypoxia (limited diffusion), and acute hypoxia (transient disruptions in perfusion), but this manual annotation requires an expertise that is generally not available in clinical settings.

Therefore, in this paper, we propose a new methodology that automates this annotation. The major challenge is that the training set comprises weakly labeled samples that only contains the number of MCSU types per sample, which means that we do not have the underlying structure of MCSU locations and classifications. Hence, we formulate this problem as a latent structured output learning that minimizes a high order loss function based on the number of MCSU types, where the underlying MCSU structure is exible in terms of number of nodes and connections. Using a database of 89 pairs of weakly annotated images (from eight tumors), we show that our methodology produces highly correlated number and proportion of MCSU types compared to the manual annotations.

Keyword: - Weakly Supervised Training, Latent Structured Output Learning, High order loss function.

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1. INTRODUCTION

The majority of human tumours contain chronic (limitations in oxygen diffusion)and acute (local radiotherapy and chemotherapy . While chronic hypoxia (CH) promotes the death of normal and tumor cells , acute hypoxia (AH) leads to tumor aggressiveness, so it is important to estimate the number and proportion of hypoxic regions in tumors to improve the clinical prognosis of such treatments . Matei et al. proposed a manual annotation of the number and proportion of hypoxic regions using (immune-)fluorescence (IF) and hematoxylin and eosin (HE) stained images of a histological specimen, involving the following steps (Fig. 1): 1) registration of the IF and HE images; 2) delineation of the vital tumor region; 3) detection of microcirculatory sup-ply units (MCSU), which are areas supplied by micro vessels; 4) classification of MCSUs into normoxia (N - normal oxygenation supply), CH or AH; and 5) computation of the number and proportion of MCSU types. This annotation requires expertise that is generally not available in clinical settings, which makes it a good candidate for automation. A major hurdle is that this annotation contains only the _nal number and proportion of MCSU types, without indication of MCSU locations, sizes and labels (an MCSU has size of around 200 µm and class appearance as denied in Fig. 2). Therefore, this is a weakly supervised and multi-class structured learning problem that is formulated in this paper as a latent structured output problem that minimizes a high order loss function based on the mismatch between the manual and automated estimation of the number of MCSU types, where this latent structure is exible in terms of the connections and number of MCSUs.

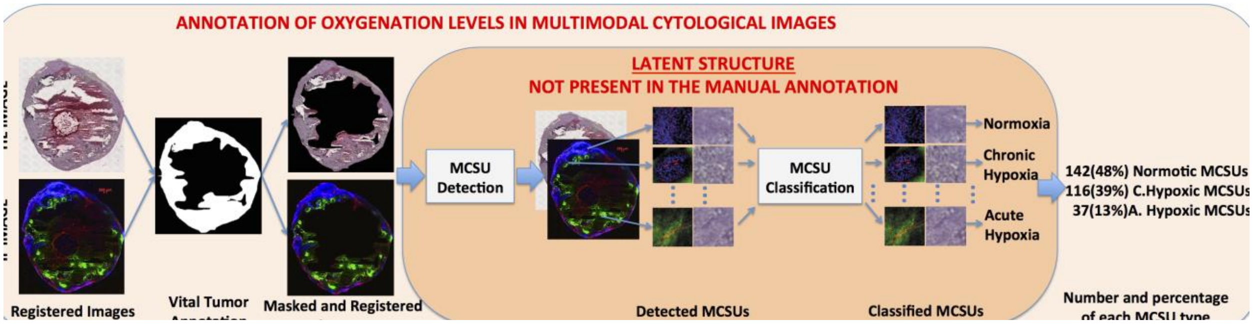

Fig. 1: Manual annotation using the HE and IF images as inputs and producing a count and proportion of the MCSU types present in the histological specimen.

.2. LITERATURE SURVEY

Although new, our problem is similar the segmentation of brain structures , involving a detection of sparse structures and multiclass classification. However, deferent from our problem, the segmentation of brain structures is formulated as a strongly supervised problem, where it is possible to use the position and shape priors. The detection of lymph nodes also deals with the identification of sparse structures without priors. In contrast to our problem, lymph node detection is strongly supervised and concerns a binary classification problem.

The automated detection and localization of multiple organs also deals with sparse detection and multi-class classification, but it is strongly supervised and one can use position and shape priors. There are a few problems formulated as weakly supervised latent structured output learning but they present some differences compared to our problem, as detailed below. The tracking of Flexible and Latent Structured Output Learning 3 indistinguishable translucent objects uses a stronger and lower level annotation, consisting of the identification of the objects before and after occlusion. In the semantic segmentation images are annotated with a set of classes, where the pixel-level annotation is not available, but these methodologies use lower level loss functions and deal with non-sparse segmentation problems.

Contributions: Our contribution is a new weakly supervised latent structured output learning methodology for the detection and multi-class classification of sparse structures in multimodal cytological images that is trained with the minimization of a high order loss function, where the main novelty is the exible structure of the latent MCSU structure in terms of number of nodes and connections. In addition, this is the _rst methodology for the automated classification of oxygenation levels in multimodal cytological images. We analised a database of 89 pairs of IF and HE images (from eight tumors), where 16 pairs of images from two tumors were for training local MCSU multi-class classi_ers, and 73 pairs of images from six tumors were for training and testing the la- tent structured output learning methodology. Using a leave-one-tumor-out cross validation experiment, we obtain a high correlation between the manual and automated annotations in terms of the number and proportion of MCSU type

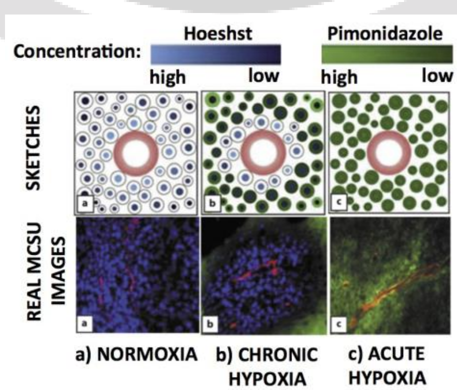

Fig. 2: MCSU classes appearance [2].

3. PROPOSED SYSTEM

1. The methodologies proposed in this paper receive as input the IF and HE images.
2. Then microvessel pixels are detected and classified.
3. Then for the FLSSVM (top) the graph is built and labelled using the initial graph in order to represent the MCSUs .
4. DCNN, a series of convolutional layers applied to the microvessel pixel classification images produce a final map containing the MCSUs and their classes.
5. From the outputs of FLSSVM and DCNN, it is trivial to obtain the final annotation

This figure is better visualised with a pdf reader - please zoom in the IF/HE images to notice the MCSU annotation

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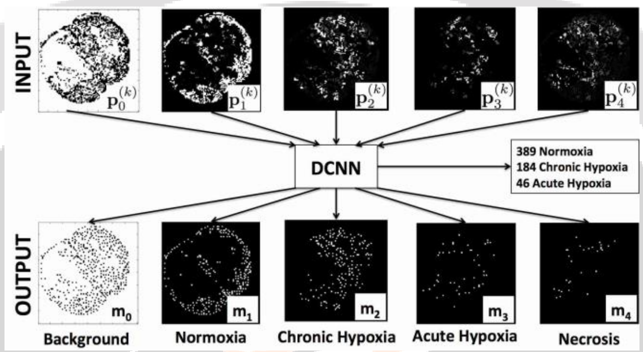


Fig 2: Output of DCNN

4. Module Description

We assume the availability of a dataset represented by the input IF and HE images, with x(IF); x(HE) is a mask that selects regions of the images that contain vital tumour tissue, and denotes the annotation of the number of normoxic (N), chronic hypoxic (CH) and acute hypoxic (AH) MCSUs.
The starting point for our proposed methodologies is the detection and multi-class classification of microvessel pixels from multimodal images , which is detailed in Sec. 4.1. This is followed by the explanation of FLSSVM in Sec. 4.2 and DCNN in Sec. 4.3.

4.1) Microvessel Pixel Detection and Classification

An MCSU is defined as a vital tumour tissue area supplied by a microvessel , which has a size of roughly 200* 200µm. Microvessel pixels are trivially detected using a threshold on the red channel of the IF image, given that microvessels have a red color in this image modality. The following are multi-class classifiers: 1) Adaboost , 2) linear SVM , 3) random forest , and 4) convolutional neural networks . The features used by classifiers 1-3 above are represented by a set of three histograms from the RGB channels of the IF and HE images and for classifier 4, the features are the RGB values from the vectorized Patch.

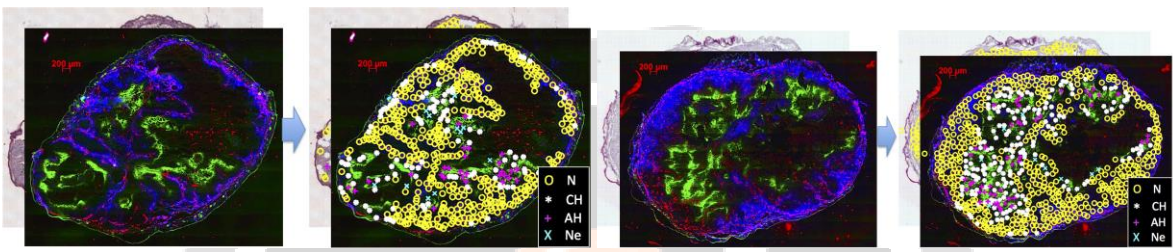
4.2) Flexible Latent Structure Support Vector Machine (FLSSVM)

The FLSSVM formulation takes as input the microvessel pixel detection and classification from above, where the goal is to build the graph G = (V; E) representing the spatial distribution and classification of MCSUs in the image, and use this graph as a hidden variable in a latent structured SVM model that is learned using a high order loss function.

4.3) Deep Convolutional Neural Network (DCNN)

The DCNN model uses as input the maps produced by the four classifiers from , which means that the input has 20 channels (four classifiers, each with the output results for five classes)

The quantitative experiment assesses the correlation of the number and proportion of MCSU classes (only for N, CH and AH) between manual and estimated annotations from the proposed FLSSVM and DCNN models in the six test sets (for the six fold cross validation) with the Bland Altman plots , which display the number of samples, Sum of squared error (SSE), Pearson r-value squared (r2),linear regr ession, and p-value.



Ground Truth: N = 473(72%), CH = 158(24%), AH = 25(4%) Ground Truth: N = 510(62%), CH = 250(30%), AH = 65(8%)
Detection: N = 423(75%), CH = 111(20%), AH = 29(5%) Detection: N = 484(67%), CH = 196(27%), AH = 47(6%)

Fig. 5: Automated annotations produced by the proposed methodology. Please see additional results on the supplementary material.

5. CONCLUSION

The qualitative results in Fig. 5 show that our final classification results are similar to the ground truth annotation. These results provide evidence that our approach is potentially useful in a clinical setting for the automated annotation of oxygenation levels in multimodal cytological images.

6. REFERENCES

[1] Gustavo Carneiro, Tingying Peng, Christine Bayer, Nassir Navab "Automatic Quantification of Tumour Hypoxia from Multi-modal Microscopy Images using Weakly-Supervised Learning Methods ",IEEE TRANSACTIONS ON MEDICAL IMAGING .

[2] G. Carneiro, T. Peng, C. Bayer, and N. Navab. "Flexible and latent structured output learning". In International Workshop on Machine Learning in Medical Imaging, pages 220–228. Springer, 2015.

[3] G. Carneiro, T. Peng, C. Bayer, and N. Navab. "Weakly-supervised structured output learning with flexible and latent graphs using high-order loss functions". In Proceedings of the IEEE International Conference on Computer Vision, pages 648–656, 2015.

BIOGRAPHIES

Adsure Sonali is pursuing M.E Computer Engg in VACOEA,Ahmednagar. Her areas of research interests include Medical Images ,Image Processing.