Proceedings Paper:
Breen, J orcid.org/0000-0002-9020-3383, Zucker, K orcid.org/0000-0003-4385-3153, Orsi, NM et al. (1 more author) (2022) Assessing Domain Adaptation Techniques for Mitosis Detection in Multi-scanner Breast Cancer Histopathology Images. In: MICCAI 2021: Biomedical Image Registration, Domain Generalisation and Out-of-Distribution Analysis. MICCAI 2021, 27 Sep - 01 Oct 2021, Strasbourg, France. Springer, Cham , pp. 14-22. ISBN 9783030972806

https://doi.org/10.1007/978-3-030-97281-3_2

Assessing domain adaptation techniques for mitosis detection in multi-scanner breast cancer histopathology images

JACK BREEN[1], KIERAN ZUCKER[2], NICOLAS ORSI[2], GEOFF HALL[2], and NISHANT RAVIKUMAR[1],

[1]CISTIB Centre for Computational Imaging and Simulation Technologies in Biomedicine, School of Computing, University of Leeds, UK and

[2]Leeds Institute of Medical Research at St James's, School of Medicine, University of Leeds, UK

1 ABSTRACT

Breast cancer is the most prevalent cancer worldwide and over two million new cases are diagnosed each year [Sung et al. 2021]. As part of the tumour grading process, histopathologists manually count how many cells are dividing, in a biological process called mitosis. Artificial intelligence (AI) methods have been developed to automatically detect mitotic figures, however these methods often perform poorly when applied to data from outside of the original (training) domain, i.e. they do not generalise well to histology images created using varied staining protocols or digitised using different scanners. Style transfer, a form of domain adaptation, provides the means to transform images from different domains to a shared visual appearance and have been adopted in various applications to mitigate the issue of domain shift. In this paper we train two mitosis detection models and two style transfer methods and evaluate the usefulness of the latter for improving mitosis detection performance in images digitised using different scanners. We found that the best of these models, U-Net without style transfer, achieved an F1-score of 0.693 on the MIDOG 2021 preliminary test set.

2 METHODS

Style transfer is a type of domain adaptation which focuses on the visual appearance of an image. These methods take a content image and one or more style images, and create a stylised representation of the former. We evaluated style transfer on two detection methods, a U-Net with ResNet152 encoder [Ronneberger et al. 2015] and a RetinaNet with ResNet101 encoder [Lin et al. 2020]. Two methods of style transfer were examined for pre-processing data from an unseen scanner: neural style transfer and CycleGAN. Due to the large size of the input images, all training and testing was undertaken using 512x512 patches.

To evaluate our methods we took a three-fold approach where two annotated scanners would be used for training and the other would be used for testing. These models were each evaluated using the cell-wise F1-score with a similar implementation to that of MIDOG Challenge 2021.

2.1 Mitosis Detection Models

We use a typical U-Net [Ronneberger et al. 2015] with an implementation built upon a pneumothorax segmentation model [Anuar 2019] which combines binary cross entropy loss, dice loss and focal loss. U-Net requires segmentation masks for training, which we generated by taking each pixel to be a 1 if it was within a mitotic figure bounding box and a 0 otherwise. The model outputs a probability map, which were converted to bounding boxes through a multi-step process - first a binary map was generated by applying a threshold to the probability map, then objects were detected using OpenCV to select external contours. Any detection with a height or width less than 10 pixels was assumed to be

an artifact and was removed. The remaining detections have a bounding box placed around their centre at the same size as the originally provided bounding boxes.

Our RetinaNet model implementation was based on a demonstration of it performing comparably to an expert pathologist for quantifying equine pulmonary hemosiderophages in H&E stained images [Marzahl et al. 2020].

2.2 Style Transfer

2.2.1 Neural Style Transfer. Neural style transfer is a one-to-one style transfer method, meaning it casts the style from one image (the style image) onto the content of another (the content image) [Gatys et al. 2016]. This method uses intermediate layers of a VGG19 CNN for feature extraction, generating a style representation and a content representation of each input image. The loss function combines a style loss and a content loss.

2.2.2 CycleGAN. CycleGAN is a generative adversarial network-driven unpaired image-to-image translation model [Zhu et al. 2017]. CycleGAN trains two generators simultaneously, one mapping images from domain A to domain B, and the other mapping images from domain B to domain A, each using a standard GAN adversarial loss to quantify the similarity between the output image and other images in the target domain. This architecture is designed to overcome mode collapse, where a generator produces the same output regardless of the input. To do this, the model trains in a cyclic fashion, where the input image is mapped from domain A to domain B through the first generator then back to domain A with the second generator. A cycle-consistency loss compares the original input image to the reconstructed image from the generators to ensure content information is not lost through the stylisation process. We train CycleGAN for 50 epochs on 512x512 patches taken from 10 WSIs from each domain using the original author's Pytorch implementation [Zhu et al. 2021].

2.2.3 MIDOG Challenge Submission. Our final submission is a U-Net without style transfer as both methods evaluated were not found to deliver consistent benefits to mitosis detection. This is trained on annotated data acquired using all three scanners, namely, Hamamatsu S360, Hamamatsu XR and Aperio CS.

3 RESULTS

Table 1. F1 scores from U-Net detection model

	Training scanners		Unseen scanner		
Unseen Scanner	Training set	Test set	Baseline	Neural Style Transfer	CycleGAN
Hamamatsu S360	0.760	0.731	0.661	0.593	0.558
Hamamatsu XR	0.707	0.671	0.508	0.491	0.556
Aperio CS	0.697	0.675	0.686	0.701	0.594
Average	0.721	0.692	0.618	0.595	0.569

Table 2. F1 scores from RetinaNet detection model

	Training scanners		Unseen scanner		
F1 scores	Training set	Test set	Baseline	Neural Style Transfer	CycleGAN
Hamamatsu S360	0.763	0.655	0.673	0.680	0.637
Hamamatsu XR	0.751	0.827	0.462	0.450	0.294
Aperio CS	0.804	0.699	0.675	0.704	0.759
Average	0.773	0.727	0.603	0.611	0.563

4 DISCUSSION AND CONCLUSION

Pathologists have been evaluated at a cell-wise F1-score of 0.68 for mitosis detection [Marzahl et al. 2020]. Both of our detection models performed at an expert level on the training domain data data, with an average F1-score of 0.73 for RetinaNet and 0.69 for U-Net. The performance drops for both models on data from a previously unseen scanner, with average F1-scores dropping to 0.60 and 0.62 for RetinaNet and U-Net respectively. Detection was particularly poor when Hamamatsu XR was the unseen scanner, which may be caused by the darker purple colour of the scans produced on this scanner, which leads to false positives as mitotic figures are typically a dark purple colour in H&E scans.

The methods of style transfer evaluated performed inconsistently, with each method giving an improvement over the baseline score for at least one unseen scanner but degrading average performance for all except neural style transfer on RetinaNet. This partial success justifies the need for further investigations to understand the inconsistency of the style transfer methods.

REFERENCES

Anuar, A. [2019]. Siim–acr pneumothorax segmentation.
URL: *https://github.com/sneddy/pneumothorax-segmentation*

Gatys, L., Ecker, A. and Bethge, M. [2016]. A neural algorithm of artistic style *Journal of Vision* **16**.

Lin, T. Y., Goyal, P., Girshick, R., He, K. and Dollar, P. [2020]. Focal loss for dense object detection *IEEE Transactions on Pattern Analysis and Machine Intelligence* **42**.

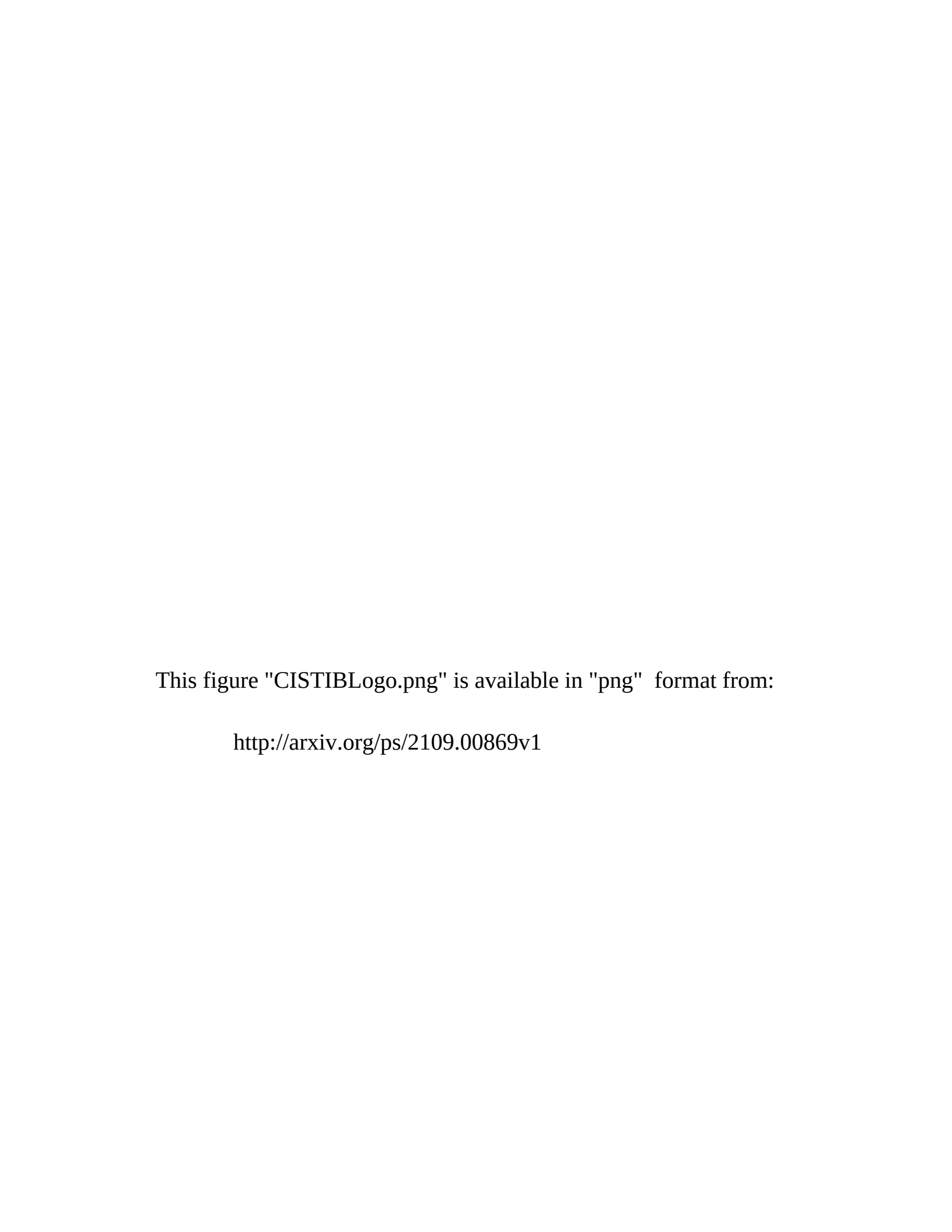
Marzahl, C., Aubreville, M., Bertram, C. A., Stayt, J., Jasensky, A.-K., Bartenschlager, F., Fragoso-Garcia, M., Barton, A. K., Elsemann, S., Jabari, S., Krauth, J., Madhu, P., Voigt, J., Hill, J., Klopfleisch, R. and Maier, A. [2020]. Deep learning-based quantification of pulmonary hemosiderophages in cytology slides *Scientific Reports* **10**, 9795.
URL: *https://doi.org/10.1038/s41598-020-65958-2*

Ronneberger, O., Fischer, P. and Brox, T. [2015]. U-net: Convolutional networks for biomedical image segmentation Vol. 9351 ,.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. [2021]. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries *CA: A Cancer Journal for Clinicians* **71**.

Zhu, J. Y., Park, T., Isola, P. and Efros, A. A. [2017]. Unpaired image-to-image translation using cycle-consistent adversarial networks Vol. 2017-October ,.

Zhu, J.-Y., Park, T. and Wang, T. [2021]. Cyclegan and pix2pix in pytorch.
URL: *https://github.com/junyanz/pytorch-CycleGAN-and-pix2pix*


This figure "CISTIBLogo.png" is available in "png" format from:
http://arxiv.org/ps/2109.00869v1

This figure "ColourDist.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "LeastAnnos.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "LeedsLogo.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "MostAnnos.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "NST_Gatys.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "PredMap.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "ThreshMap.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "U-Net_Diagram.PNG" is available in "PNG" format from:

http://arxiv.org/ps/2109.00869v1

This figure "bbox.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "content.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "image_crops.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "image_crops_wide.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "style.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "stylised.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1

This figure "truth.png" is available in "png" format from:

http://arxiv.org/ps/2109.00869v1