Deep learning-based transformation of H&E stained tissues into special stains

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Table of contents

01

Introduction

Introduction

- Histological analysis of stained human tissue samples is the gold standard for evaluation of many diseases.
- The most common stain (otherwise referred to as the routine stain) is the hematoxylin and eosin (H&E), covering ~80% of all the human tissue staining performed globally.
- H&E stain is relatively easy to perform and is widely used across the industry.

Introduction

- There are a variety of other histological stains with different properties.
- Some type staining:
  - Masson’s trichrome (MT) stain is used to view connective tissue.
  - periodic acid-Schiff (PAS) can be used to better scrutinize basement membranes.
  - Jones methenamine silver (JMS) stain offers a sharp contrast to visualize glomerular architecture.
- These features have importance for certain disease types such as nonneoplastic kidney disease.
- These non-H&E stains are also called special stains

Introduction

- While H&E staining is performed using a streamlined staining procedure, the special stains often require more preparation time, effort, and monitoring by a histotechnologist, which increases the cost of the procedure and takes additional time to produce.
- More recently, computational staining techniques known as virtual staining have been developed. Using deep learning, virtual staining has been applied on label-free. (such as autofluorescence)
- An alternative approach that can be used to bypass histochemical tissue staining is to computationally transform the WSI of an already stained tissue into another stain

02

Architecture

Stain Transformation Network

- In this paper, we present a supervised deep learning-based stain transformation framework, outlined in Fig. 1. The training of this technique is based on spatially-registered. ~minimum matching loss (perfectly paired)

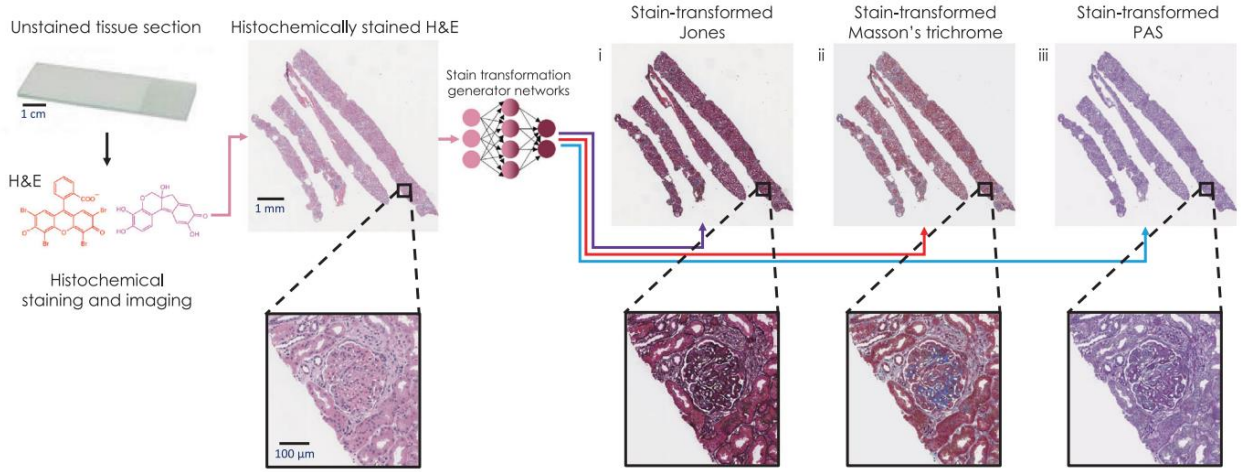


Fig. 1 Overview of deep learning-based H&E stain transformation into special stains. Histochemical staining of H&E is digitally transformed using a deep neural network into the special stains: (i) generation of JMS (purple arrow); (ii) generation of MT (red arrow); (iii) generation of PAS (blue arrow).

Stain Transformation Network

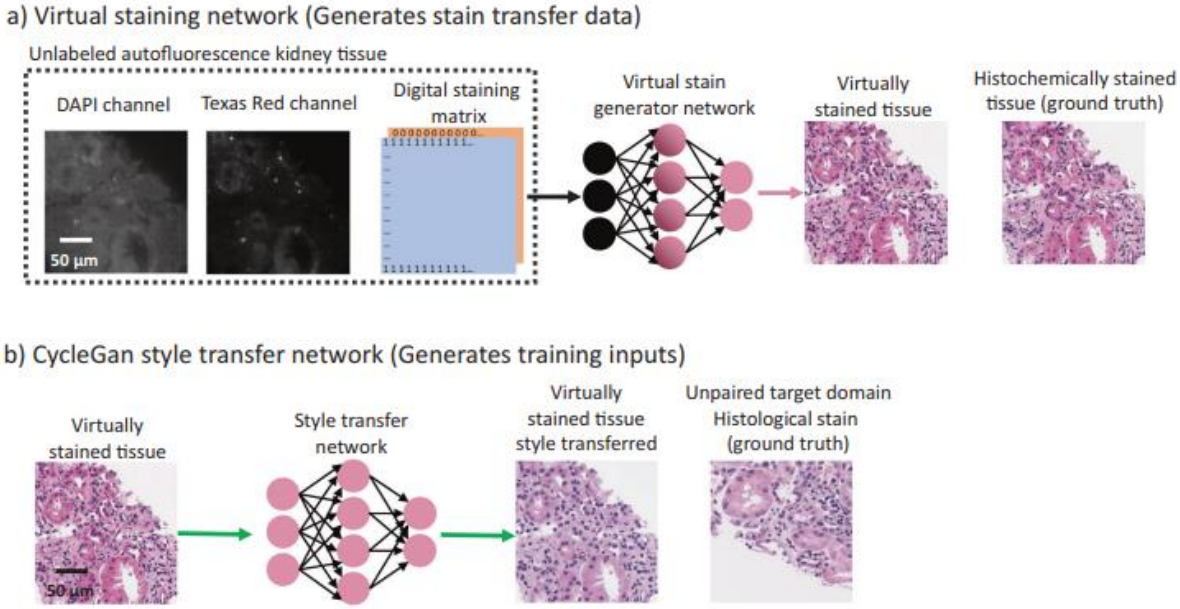
- It uses GANs. Each of these GANs consists of a generator (G) and a discriminator (D).
- This GAN loss is used in conjunction with two additional losses: a mean absolute error (L1) loss and a total variation (TV) loss.
- L1 loss is used to ensure that the transformations are performed accurately in space and color.
- the TV loss is used as a regularizer, and reduces noise created by the GAN loss.
- Generator: a modified U-net neural network
- Discriminator: a VGG-style network

Style Transfer Network (Augmentation)

- The H&E stain images must be augmented with additional staining styles to ensure generalization. In other words, we designed our network to be able to handle inevitable variability in histochemical H&E staining.
  - (i) differing staining procedures and reagents among histotechnologists and pathology labs.
  - (ii) differences among digital WSI scanners that are being used.

- CycleGAN ~ unpaired data

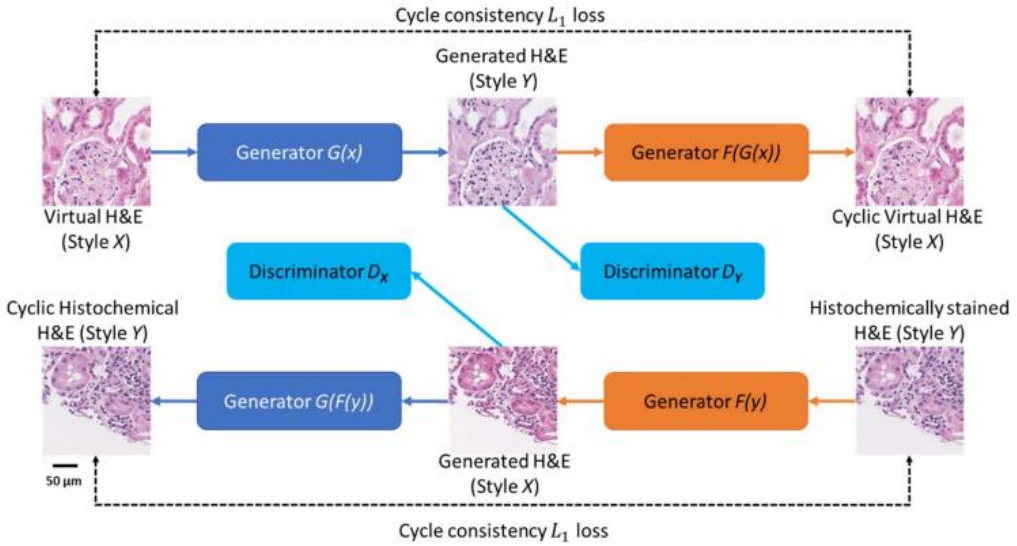
Style Transfer Network (Augmentation)



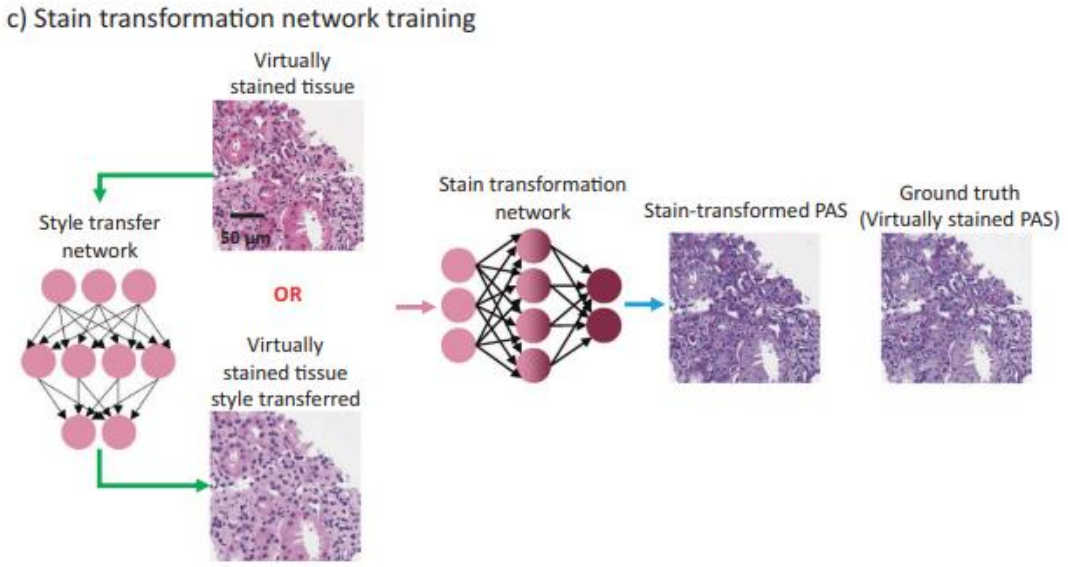
Style Transfer Network (Augmentation)

- CycleGAN model to augment the training dataset by performing style transfer.
- map between two domains X and Y
- This model performs two mappings G : X -> Y and F : Y -> X
- two adversarial discriminators D_X and D_Y are introduced

Style Transfer Network (Augmentation)



Stain Transformation Network



03

Evaluation

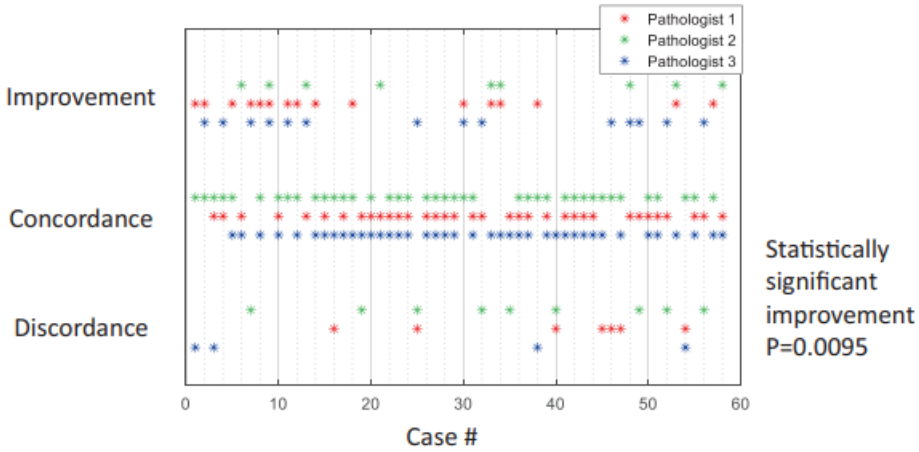
Evaluation

- Three pathologists filled out diagnostic information.

- Pahse1: diagnosis based on H&E only
- 3 weeks later
- Phase2: diagnosis based on H&E and stain-transformed special stains
- 3 weeks later
- Phase3: diagnosis based on H&E and histochemical special stains

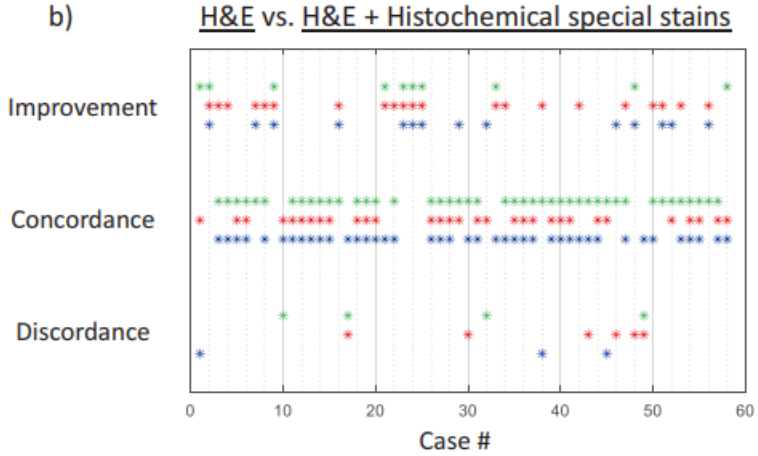
Evaluation

a)



Statistically significant improvement P=0.0095

b)



Statistically significant improvement P=0.0003

Evaluation of the quality of stain-transformed

- 3 pathologists rated the quality of various aspects of the stains generated using the stain transformation network as well as the images of histochemically stained tissue from serial tissue sections.
- The pathologists scored **four aspects** of each FOV on a scale **from 1 to 4**, where **4 is perfect**, **3 is very good**, **2 is good enough** (passable), and **1 is not acceptable**

Evaluation of the quality of stain-transformed

a) Masson's Trichrome

	Stain quality score	Nuclear detail	Cytoplasmic detail	Extracellular Fibrosis
Stain transformation	3.19	3.39	3.24	3.11
Histologically stained	3.09	2.95	3.19	3.30
Stain transformation std. error (between pathologists)	0.52	0.35	0.47	0.71
Std. error histological (between pathologists)	0.21	0.27	0.25	0.43

b) PAS

	Stain quality score	Nuclear detail	Cytoplasmic detail	Basement membrane detail
Stain transformation	3.40	3.53	3.38	3.39
Histologically stained	3.51	3.49	3.41	3.53
Stain transformation std. error (between pathologists)	0.41	0.26	0.39	0.44
Std. error histological (between pathologists)	0.33	0.33	0.42	0.33

c) Jones Silver Stain

	Stain quality score	Nuclear detail	Cytoplasmic detail	Basement membrane detail
Stain transformation	3.84	3.70	3.70	3.91
Histologically stained	3.88	3.72	3.82	3.98
Stain transformation std. error (between pathologists)	0.13	0.22	0.15	0.05
Std. error histological (between pathologists)	0.06	0.16	0.01	0.02

Resources

- de Haan, K., Zhang, Y., Zuckerman, J.E. *et al.* Deep learning-based transformation of H&E stained tissues into special stains. *Nat Commun* **12**, 4884 (2021). https://doi.org/10.1038/s41467-021-25221-2