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High-fidelity unsupervised virtual staining for digital pathology via progressive Schrödinger bridge dynamics

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Key words: Virtual staining; Unsupervised learning; Schrödinger bridge; Digital pathology; Image processing

Corresponding author: Xingye CHEN
E-mail: chenxingye@buaa.edu.cn

ORCID: https://orcid.org/0000-0001-9482-9319

Motivation

- Conventional hematoxylin and eosin (H&E) staining is destructive and labor-intensive, and prevents reuse of the same tissue for multimodal analysis.
- Supervised virtual staining often requires precisely registered autofluorescence (AF)/H&E pairs, which are difficult to acquire in practice.
- Unpaired generative adversarial network (GAN)-based translation avoids paired supervision but can suffer from instability, mode collapse, and limited structural fidelity.
- AF→H&E translation is a morphology-preserving cross-modality transport problem: appearance should change while nuclei, glandular boundaries, and stromal architecture remain faithful.
- Enhanced unpaired neural Schrödinger bridge (E-UNSB) addresses this with progressive Schrödinger bridge transport plus pathology-specific structural regularization.

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Main idea

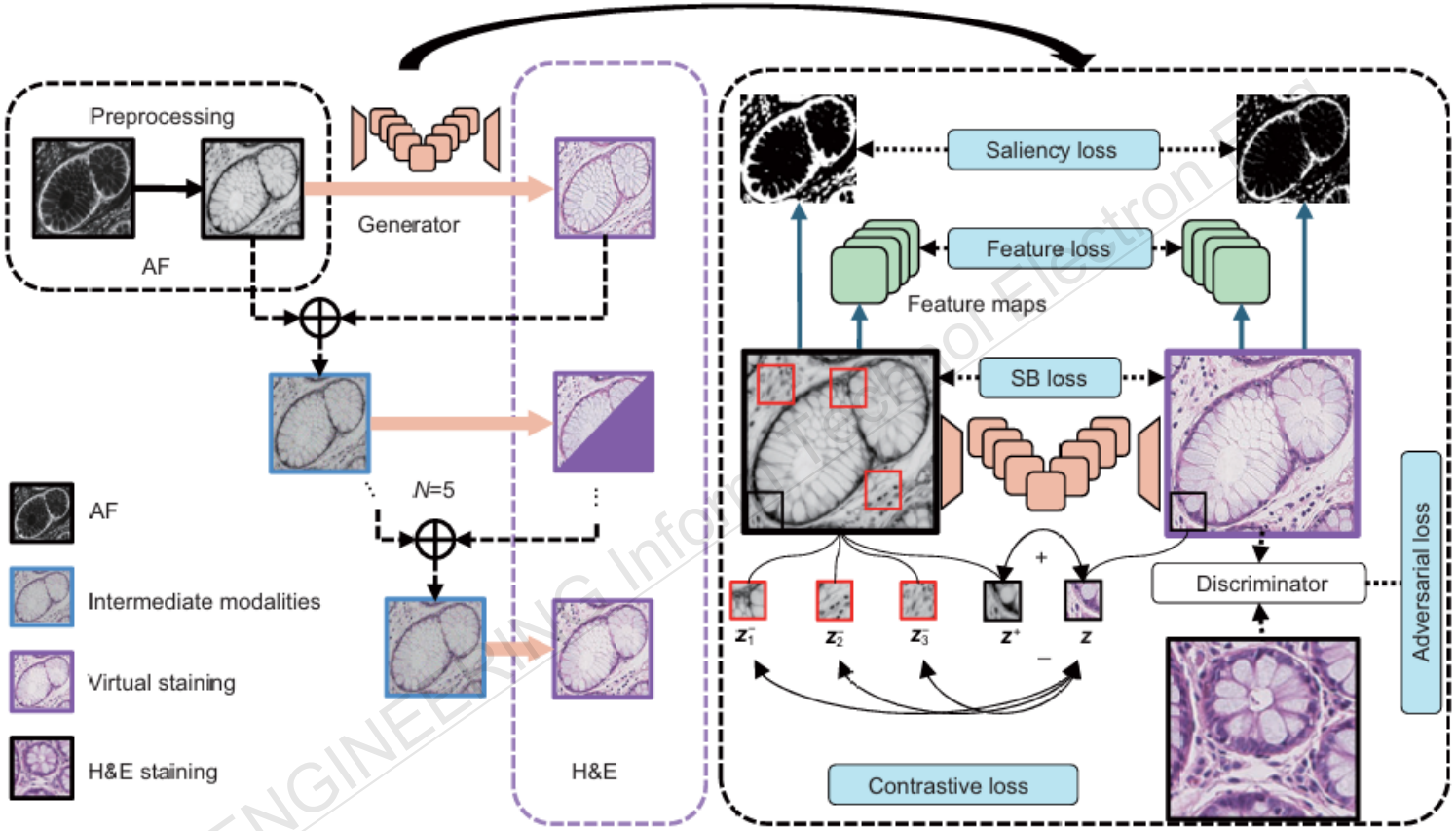
• Adapt UNSB to unsupervised AF→H&E virtual staining using a unidirectional, progressive stochastic transport process rather than a one-step domain mapping.

• Preserve pathology-relevant structure with three complementary constraints: PatchNCE for local correspondence, saliency consistency for salient tissue structures, and VGG16 feature consistency for global organization.

• Validate beyond visual quality using Fréchet inception distance (FID)/kernel inception distance (KID), QuPath morphometrics, blinded pathologist ratings, ablation/robustness studies, and an exploratory H&E→IHC-like prediction study.

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Method



Time-conditioned generator

$$G_\phi(\boldsymbol{X}_{t_i}, t_i, \boldsymbol{z})$$

Generator output at bridge time t_i, conditioned on the current state and Gaussian noise.

Total training objective

$$\mathcal{L}_{\text{total}} = \mathcal{L}_{\text{Adv}} + \lambda_{\text{SB}}\mathcal{L}_{\text{SB}} + \lambda_{\text{NCE}}\mathcal{L}_{\text{NCE}} + \lambda_{\text{Sal}}\mathcal{L}_{\text{saliency}} + \lambda_{\text{Feat}}\mathcal{L}_{\text{Feat}}.$$

Combined loss function to enhance the transformation fidelity (default bridge step number N=5)

Method

Architecture & structural regularization

Generator: 8 downsampling + 8 upsampling U-Net blocks with skip connections; channels 64→512.

Conditioning: Fourier time embedding + multilayer perceptron (MLP); Gaussian noise is mapped to affine modulation parameters.

Training losses:

- Schrödinger bridge path loss
- PatchNCE local contrastive loss
- Saliency consistency
- VGG16 global feature consistency

Training & inference

Dataset: UTOM; 20 tissue cores are split, 14 for training and 6 for test before tiling. Training yields 5372 AF and 5568 H&E patches.

Optimization: Adam (β_1=0.5, β_2=0.999), learning rate 2×10^{-4}, 100 epochs; linear decay over the last 50 epochs; batch size 4; PatchNCE τ=0.07.

Large-image inference: 256×256 tiles, stride 128 (50% overlap), with center-weighted blending.

Trainable parameters: 20.98M for E-UNSB vs 28.29M for CycleGAN.

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Key design principle: change staining appearance progressively while constraining local and global morphology.

Results

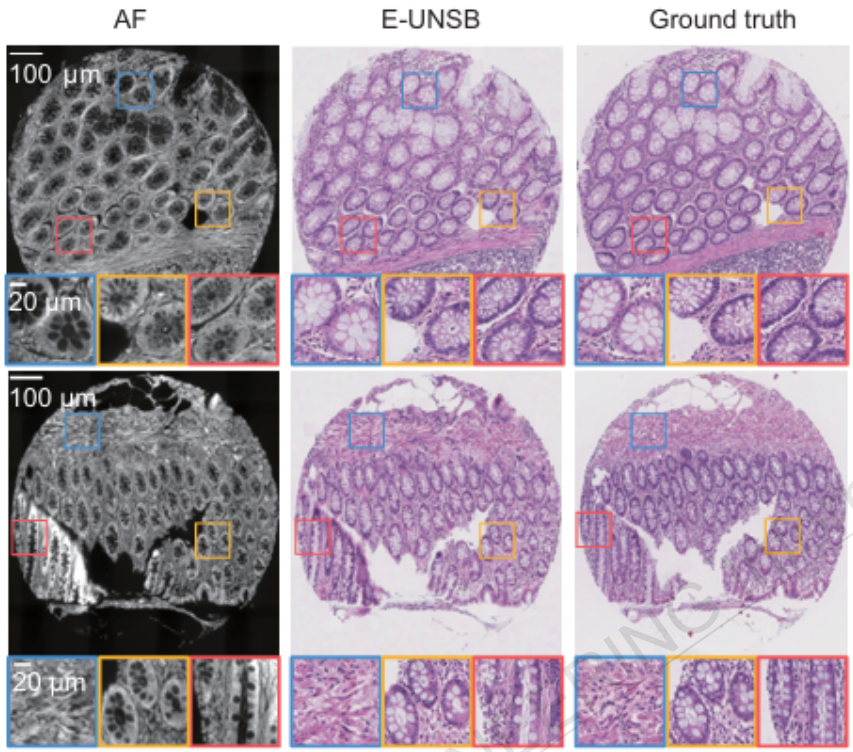


Fig. 3 AF → virtual H&E

E-UNSB preserves tissue architecture and cellular morphology, including nuclear–cytoplasmic contrast and glandular/stromal interfaces.

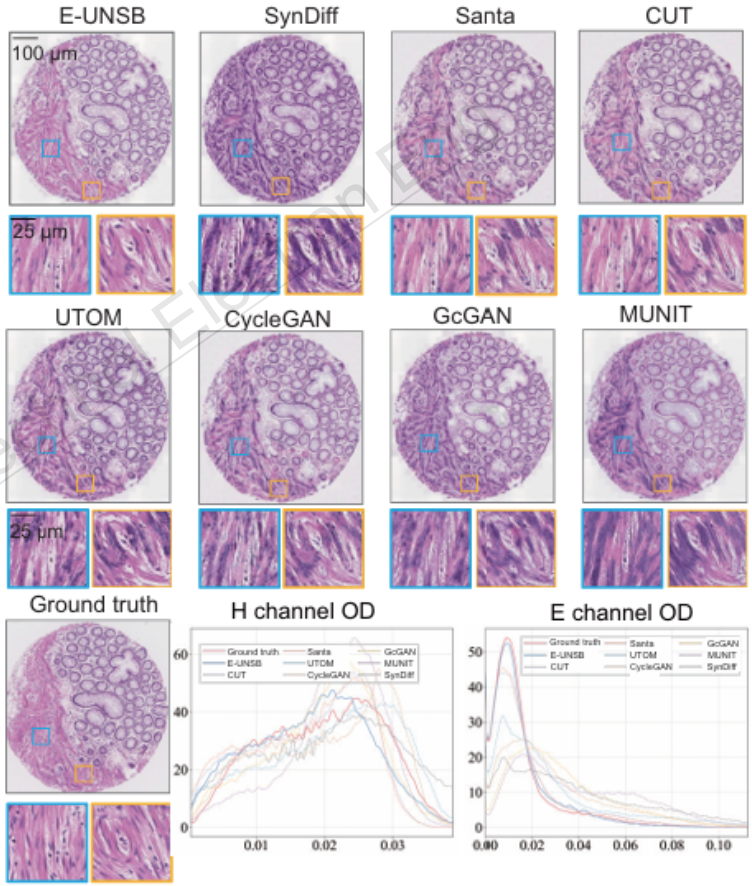
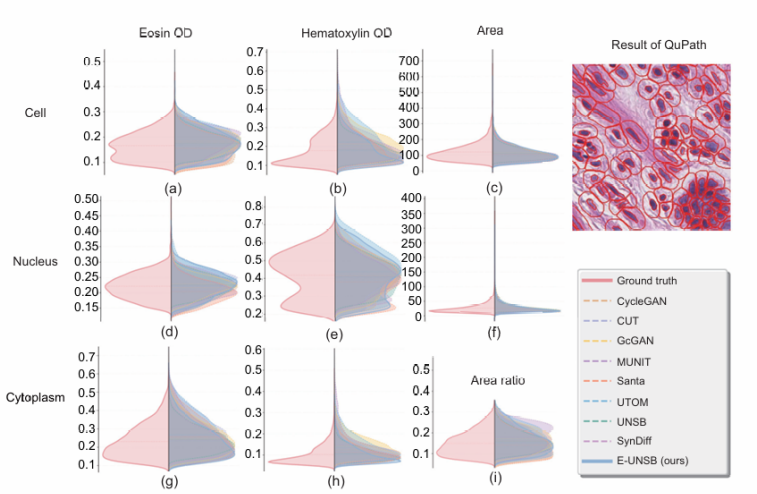
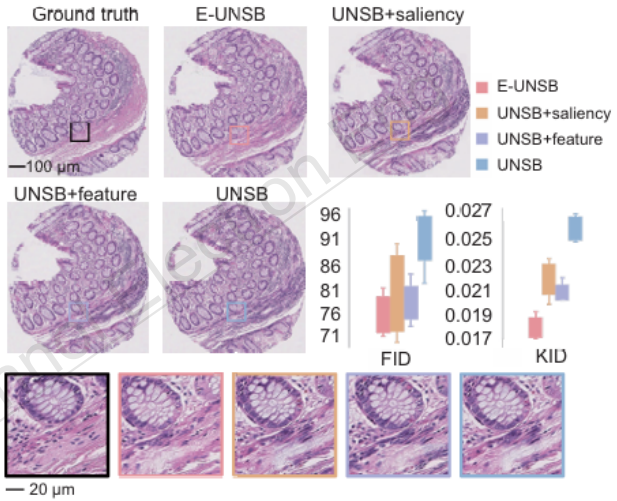


Fig. 4 Comparison with existing methods

Achieving the highest as FID=75.27±3.76 & KID=(18.1±0.9)×10^{-3}

Results





Downstream validation

E-UNSB: mean|Cohen's *d*|=0.0953; Wasserstein distance=0.7360.

UNSB: 0.1215/1.7282; SynDiff: 0.1340/1.3310.

Across nine QuPath features, E-UNSB shows the closest overall agreement with reference H&E.

Blinded pathologist study

Overall mean score: reference H&E 3.06; E-UNSB 2.80; CycleGAN 2.24; Santa 2.10. E-UNSB vs CycleGAN/Santa: adjusted $p<0.01$ across all four criteria.

Ablation study

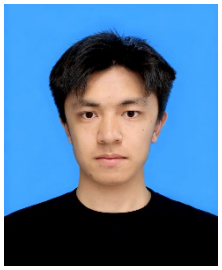
Full model: FID 75.27/KID 18.1. Without NCE: 87.53/27.4. $N=5$ was selected as the quality–runtime trade-off (21.5 ms).

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Conclusions

- E-UNSB adapts UNSB to pathology-oriented virtual staining by combining progressive Schrödinger bridge transport with local and global structural regularization.
- For AF→H&E, it achieved FID 75.27 and KID 18.1×10^{-3}, with closer QuPath morphometrics and higher blinded pathologist ratings than the evaluated baselines.
- Exploratory H&E→IHC-like results showed regional statistical similarity for CD146 and NKX3.1; these outputs are hypothesis-generating rather than replacements for experimental IHC.
- Limitations include iterative inference cost, limited tissue/device coverage, possible artifacts or hallucinated structures, and acquisition-sensitive saliency constraints.
- Future work: multicenter/cross-device validation, systematic failure analysis, uncertainty estimation, rare-structure preservation, and cell-/lesion-level validation.

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Jianqiao YE received his first BS degree in 2025 from Beihang University, China. Currently, he is pursuing his MS degree. His research interests include image process, deep learning, and clinical applications.



Xingye CHEN received his first BS degree and Ph. D. degree from the Department of Automation in Tsinghua University, China, in 2016 and 2021, respectively. Then he worked as a postdoctoral scholar in Tsinghua University. He is currently working with the School of Electronics and Information Engineering, Beihang University, Beijing, China. His research interests computational microscopy, deep learning, and biological physics.

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