Zero-Shot Denoising for Fluorescence Lifetime Imaging Microscopy with Intensity-Guided Learning

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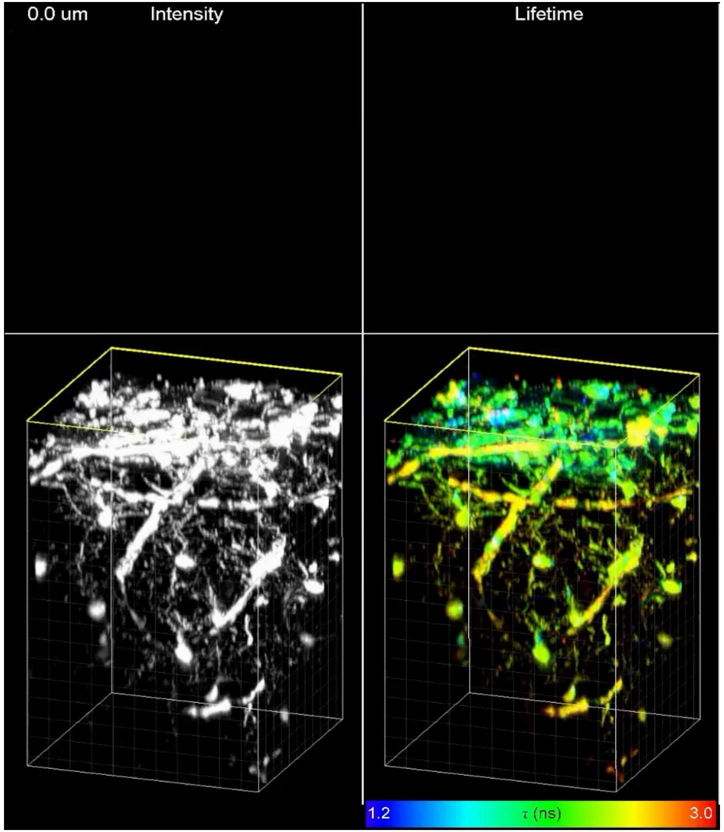
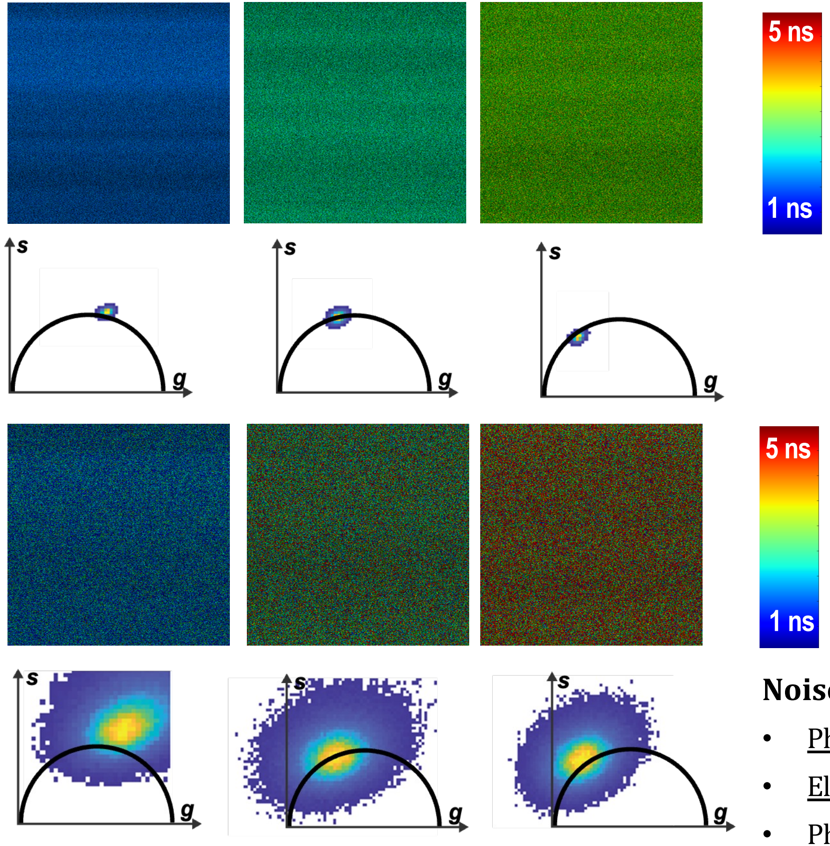
CVPR Nashville JUNE 11-15, 2025

Noisy Measurement is Everywhere



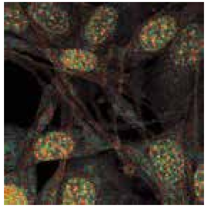
A fixed Cx3cr1-GFP/+ mouse brain (microglia labeled with EGFP; blood vessel injected with Dextran 594)

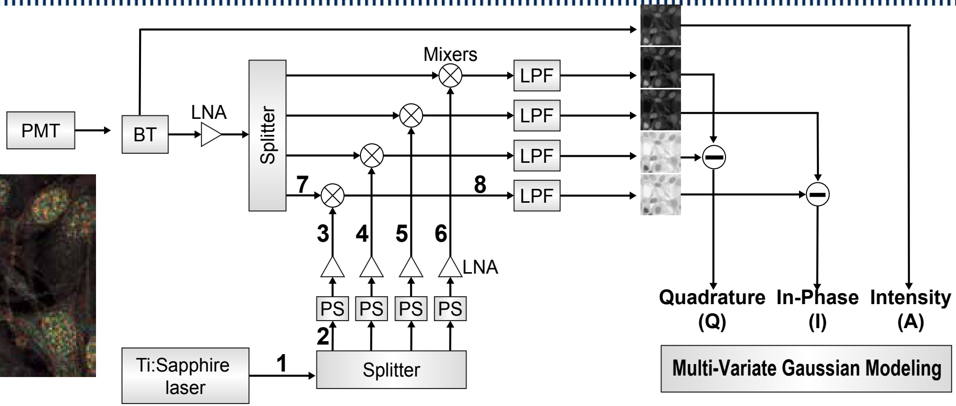


Rhodamine B | Coumarin 6 in ethanol | Fluorescein

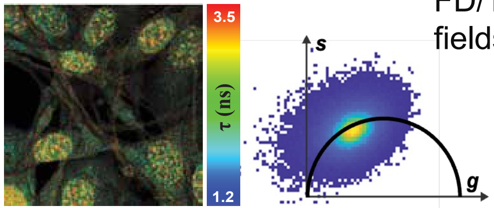
Noise Source:

- Photon Shot Noise
- Electronics Thermal Noise
- Physiological Interference
- …





Zhang, Yide, Ian H. Guldner, Evan L. Nichols, David Benirschke, Cody J. Smith, Siyuan Zhang, and Scott S. Howard. "Instant FLIM enables 4D in vivo lifetime imaging of intact and injured zebrafish and mouse brains." *Optica* 8, no. 6 (2021): 885-897.



Multi-Variate Gaussian Modeling:

- **Precise Lifetime Estimation**: Deconvolves overlapping lifetime components
- **Improved SNR for All Components**: Enhances signal clarity by reducing noise
- **Flexible and Adaptable**: Applicable for FD/TD FLIM methods and adaptable other fields.

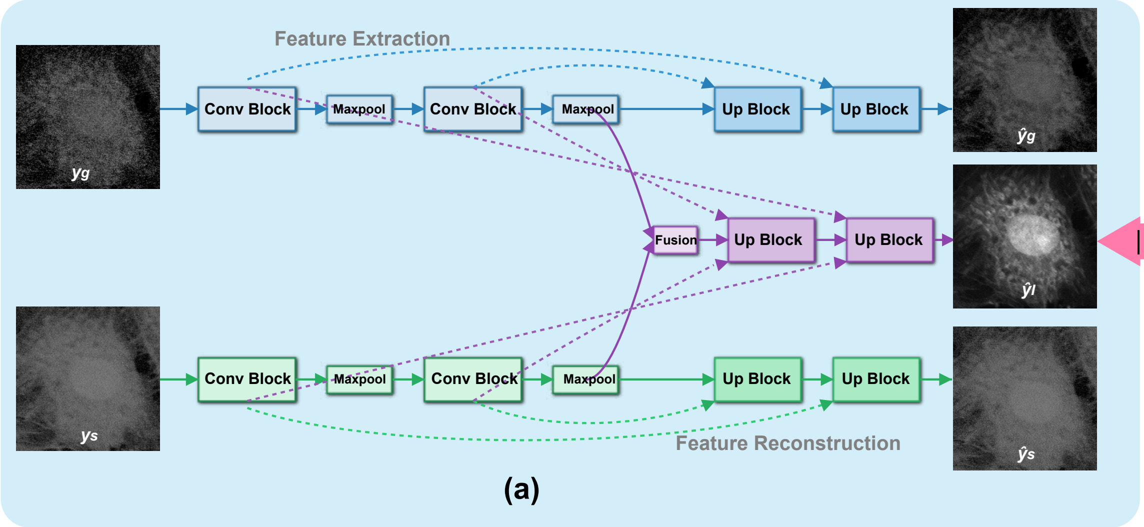
Variable	y_s	y_g	Intensity
y_s	$Var(y_s) = S_0TR^2$	$Cov(y_s, y_g) = S_0TR^2(b_2m_2\sin(\varphi_2))$	$Cov(y_s, \text{Intensity}) = S_0TR^2(b_1m_1\cos(\varphi_1))$
y_g	$Cov(y_g, y_s) = S_0TR^2(b_2m_2\sin(\varphi_2))$	$Var(y_g) = S_0TR^2$	$Cov(y_g, \text{Intensity}) = S_0TR^2(b_1m_1\sin(\varphi_1))$
Intensity	$Cov(Intensity,y_s) = S_0TR^2(b_1m_1\cos(\varphi_1))$	$Cov(Intensity,y_g) = S_0TR^2(b_1m_1\sin(\varphi_1))$	$Var(Intensity) = \S_0TR^2$

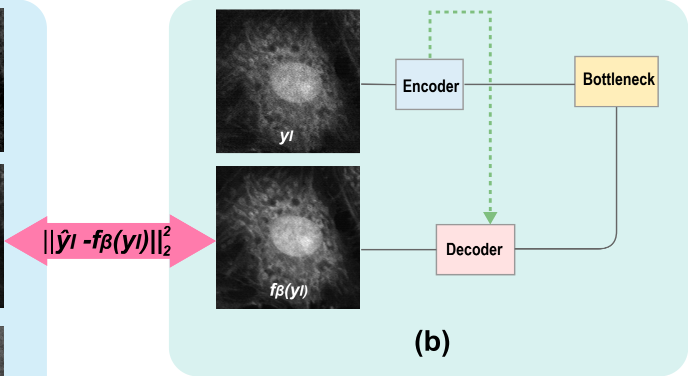
Emission Intensity **Harmonic Coefficient** **Demodulation Depth** **Phase Difference**

$$\mathrm{S(t)} = \mathrm{S}_0\left(1 + \sum_{n=1}^{\infty} b_n m_n \cos(n\omega t - \varphi_n)\right)$$

Chen, H., Geresu, D., Najera, J., Datta, M., & Howard, S. (2025, March). Experimental investigation of noise characterization in real-time, multiphoton fluorescence lifetime imaging microscopy. In Multiphoton Microscopy in the Biomedical Sciences XXV (Vol. 13324, pp. 24-29). SPIE

Better Denoising From Intensity Channel Guidance





$$\mathcal{L}_{intensity} = \|\hat{y}_I - f_\beta(y_I)\|_2^2$$

$$\mathcal{L} = \mathcal{L}_{intensity} + \lambda_1 \mathcal{L}_{fidelity} + \lambda_2 \mathcal{L}_{structure} + \lambda_3 \mathcal{L}_{TV}.$$

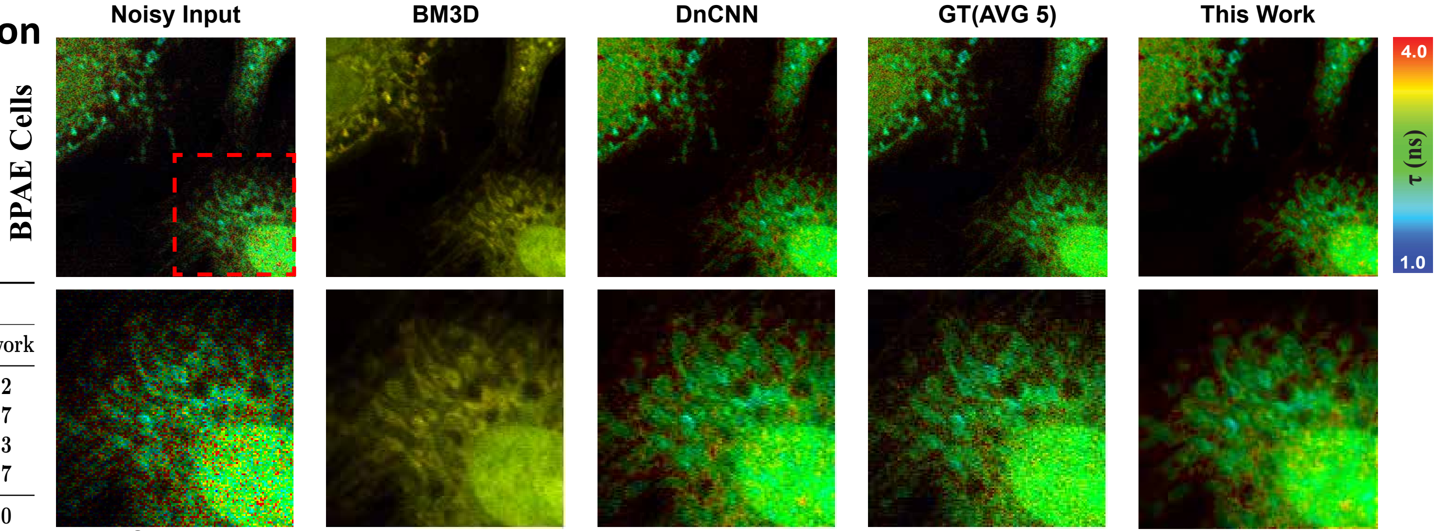
$$\mathcal{L}_{fidelity} = \|y_g - \hat{y}_g\|_2^2 + \|y_s - \hat{y}_s\|_2^2$$

$$\mathcal{L}_{structure} = [2 - \mathrm{SSIM}(\hat{y}_g, \hat{y}_I) - \mathrm{SSIM}(\hat{y}_s, \hat{y}_I)]$$

$$\mathcal{L}_{TV} = [\mathrm{TV}(\hat{y}_g) + \mathrm{TV}(\hat{y}_s)] = \sum_{i,j} \left(\left| \hat{y}_g^{i+1,j} - \hat{y}_g^{i,j} \right| + \left| \hat{y}_g^{i,j+1} - \hat{y}_g^{i,j} \right| \right) + \sum_{i,j} \left(\left| \hat{y}_s^{i+1,j} - \hat{y}_s^{i,j} \right| + \left| \hat{y}_s^{i,j+1} - \hat{y}_s^{i,j} \right| \right)$$

Sample Synthetic Illustration

$$\mathrm{PSNR}_g = \mathrm{PSNR}(y_g, \hat{y}_g)$$
$$\mathrm{PSNR}_s = \mathrm{PSNR}(y_s, \hat{y}_s)$$
$$\mathrm{PSNR}_{\mathrm{avg}} = \frac{1}{2}\left(\mathrm{PSNR}_g + \mathrm{PSNR}_s\right)$$



Sample	PSNR (dB)		
	BM3D	DnCNN	This work
In vivo Zebrafish	27.31	34.25	**37.22**
Ex vivo Mouse Kidney	41.56	46.91	**54.87**
Ex vivo BPAE	34.03	38.81	**39.13**
Fixed NIH3T3	3.30	23.41	**39.17**
Average	26.55	35.84	**42.60**

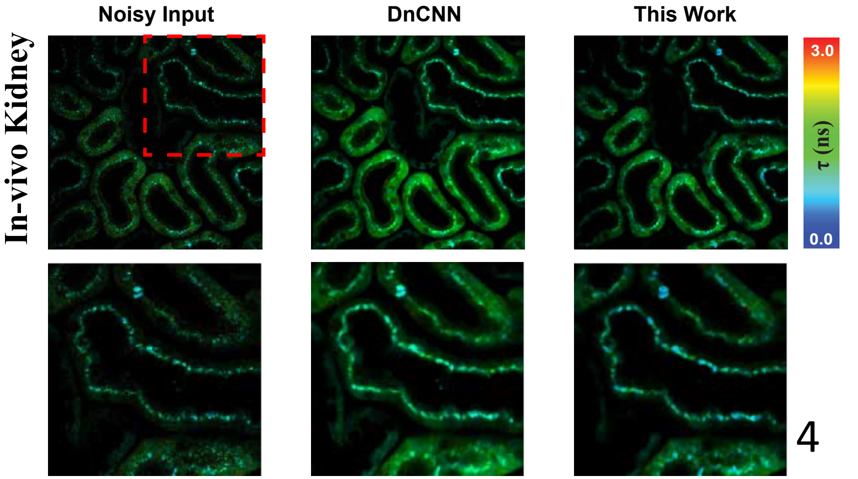
Sample	SSIM		
	BM3D	DnCNN	This work
In vivo Zebrafish	0.4100	0.7379	**0.8562**
Ex vivo Mouse Kidney	0.8450	0.9948	**0.9981**
Ex vivo BPAE	0.7053	0.7526	**0.7698**
Fixed NIH3T3	0.4016	0.6207	**0.9397**
Average	0.5905	0.7765	**0.8909**

$$\mathrm{SSIM}_g = \mathrm{SSIM}(y_g, \hat{y}_g)$$
$$\mathrm{SSIM}_s = \mathrm{SSIM}(y_s, \hat{y}_s)$$
$$\mathrm{SSIM}_{\mathrm{avg}} = \frac{1}{2}\left(\mathrm{SSIM}_g + \mathrm{SSIM}_s\right)$$

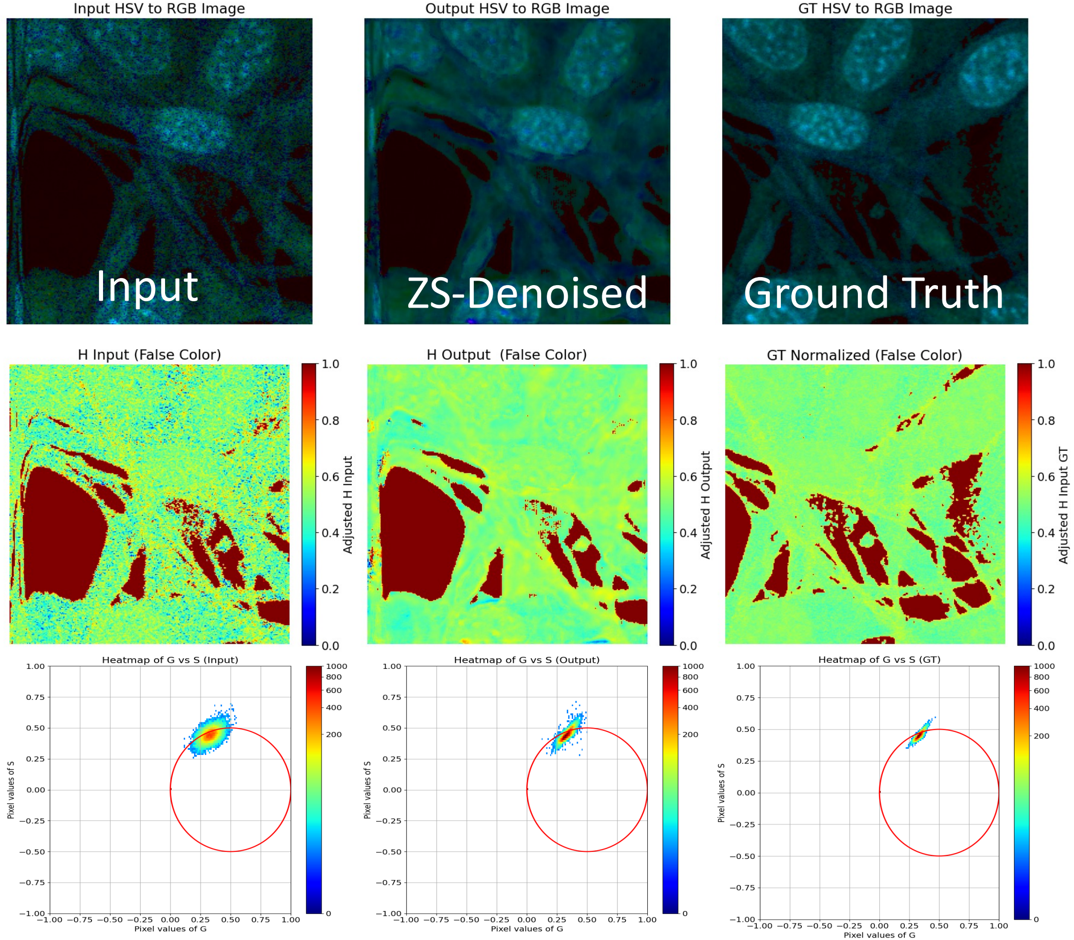
Sample	ALE (%)		
	BM3D	DnCNN	This work
In vivo Zebrafish	60.99	103.93	**56.41**
Ex vivo Mouse Kidney	23.59	11.73	**10.81**
Ex vivo BPAE	73.48	57.21	**52.60**
Fixed NIH3T3	23.93	6.09	**5.44**
Average	45.50	44.74	**31.31**

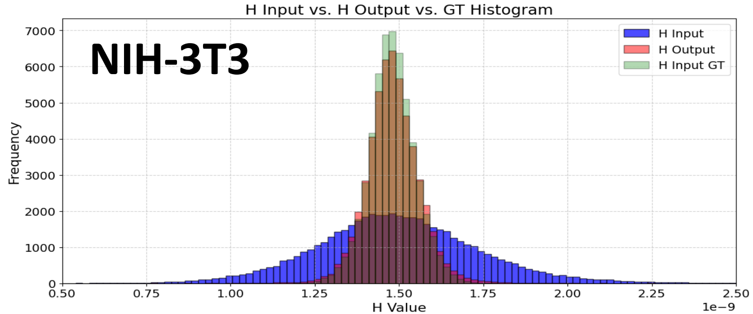
$$\tau = \frac{1}{\omega}[\mathrm{g/s}]$$

$$\overline{\tau} = \frac{1}{N}\sum_{i=1}^{M} \hat{\tau}_i$$
$$\mathrm{ALE} = \frac{1}{M}\sum_{j=1}^{M} |\hat{\tau}_j - \tau_j|$$
$$\mathrm{ALE}_{\%} = \frac{\mathrm{ALE}}{\overline{\tau}} \times 100\%$$

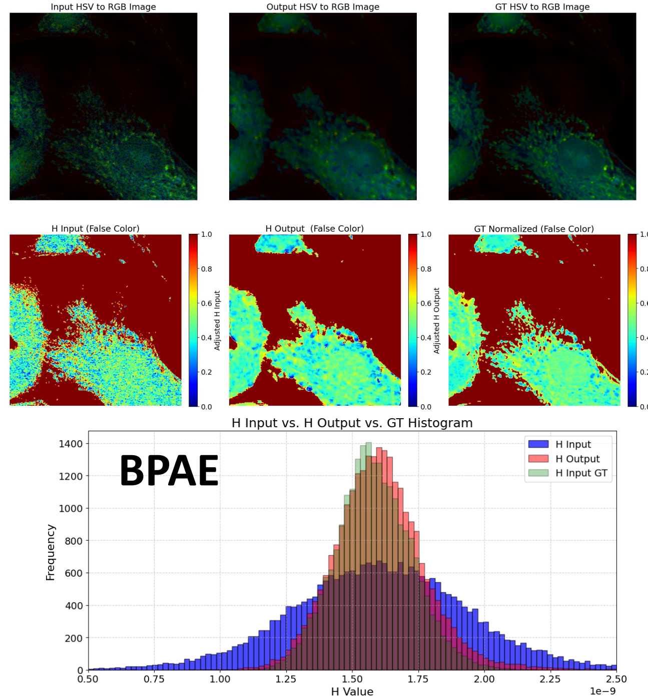


Results: NIH-3T3

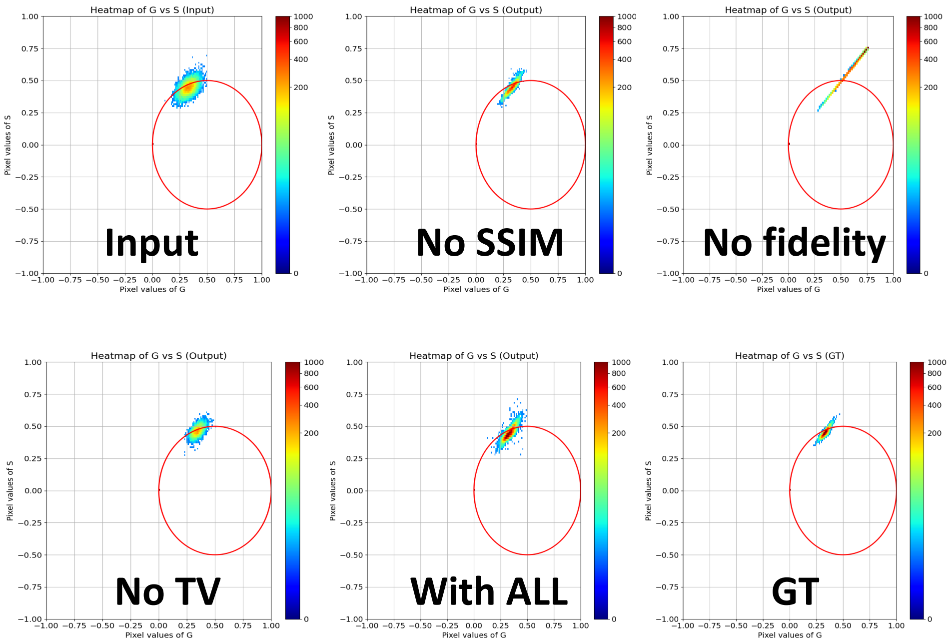


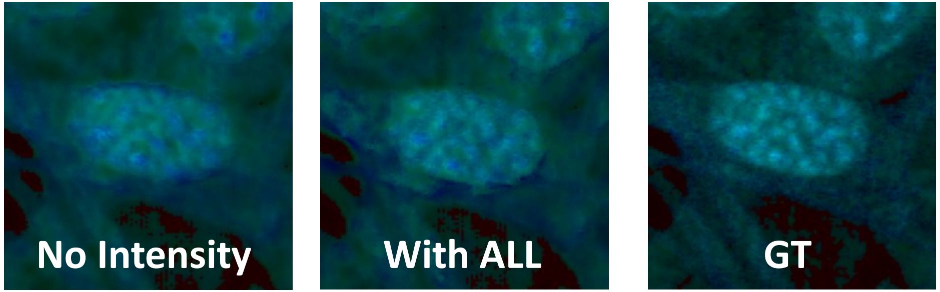


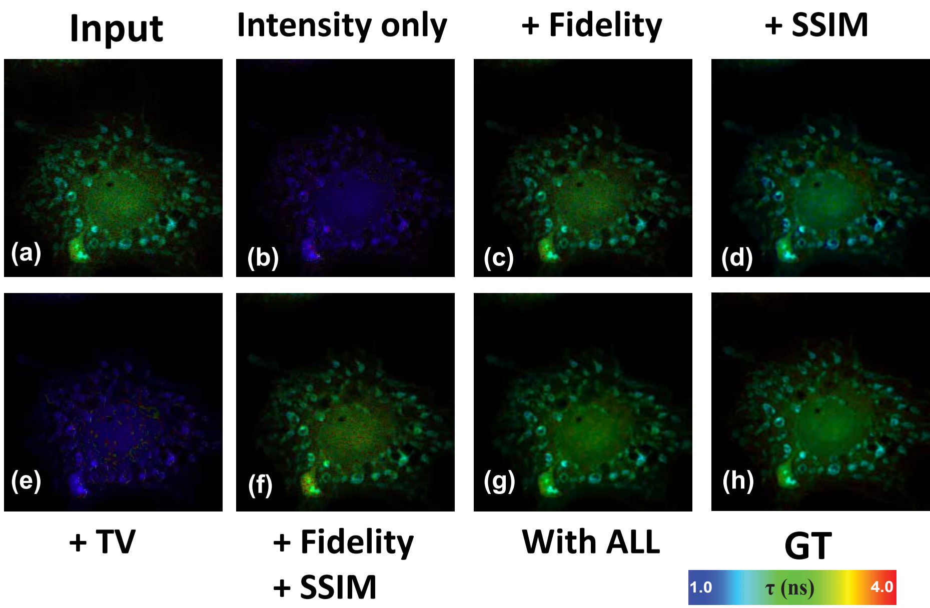
BPAE



Results: Ablation Study Of Loss Function And Intensity Guidance







Loss Configuration	PSNR ↑	SSIM ↑	ALE ↓
$\mathcal{L}_{intensity}$	33.06	0.5841	414.62
$+\lambda_1\mathcal{L}_{fidelity}$	41.34	0.8600	55.98
$+\lambda_2\mathcal{L}_{structure}$	33.29	0.7258	46.91
$+\lambda_3\mathcal{L}_{TV}$	34.23	0.6180	112.17
$+\lambda_1\mathcal{L}_{fidelity} + \lambda_2\mathcal{L}_{structure}$	41.41	0.8637	51.94
All Loss	**41.85**	**0.8810**	**34.09**

Conclusion and Discussion

- **Denoising While Preserving Lifetime Information**
- **Enhance Correlated Lifetime Channel from the Intensity**
- **Zero-shot Learning without Massive Dataset Acquiring**
- **Results Validation from Quantitative and Qualitative Illustration**

<u>Validation beyond Denoising & FLIM Task:</u>

- **Super-Resolution of FLIM**: With Super-Res guidance for the intensity channel by SRRF.
- **Deconvolution of Multimodal Microscopy** : Multivariate modeling for deconvolution.
- **Medical Imaging Reconstruction (MRI/CT)**: Multi-channel optimization with reasonable dataset.

<u>Dataset Limitation and Comparison Limitation:</u>

- **Limited Available Dataset for Comparison**: Validating mainly on published dataset.
- **Not Many Work on FLIM Denoising**: Only deep-learning-based method is DnCNN pretrained on MPG dataset.
- **Comparison of Different Intensity Guidance**: Better intensity guidance increases performance.

Thank You

Q&A