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Self-Supervised Learning for Single-Molecule Localization Microscopy

Clare Minnerath
Providence College

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Clare Minnerath, Providence College
REU: University of Colorado, Colorado Springs

What is noise?

Image Noise:

Irregular fluctuations or variation of brightness or color information in images that can obscure the bare signal.

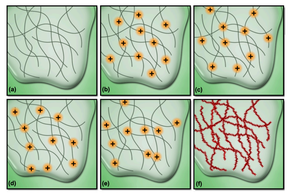
Noise Examples:

White: Digital Camera: Fixed Pattern:

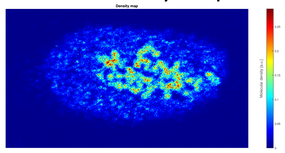
Datasets:

Single Molecule Localization Microscopy (SMLM)

- Microscopy done at the nanoscale
- Single fluorescent molecules blink on and off randomly
- Corrupted with large amounts of noise (Predominantly Poisson)
- Small Scale images taken in low light conditions (The molecules emit only a few photons)

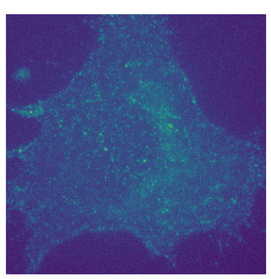


SMLM Density Map:



YFP Data:

- Dataset of yellow fluorescent protein growth factor receptors
- Emit even fewer photons per molecule than organic dyes (Low Signal to Noise Ratio – SNR)
- We use 2 of 4 separate data sets of Epithelial carcinoma cells expressing mCitrine-ErbB3
- We also Simulated these data sets using ImageJ to assess how well our denoising performed



Poisson Noise in SMLM:

- Since we only have one realization of each image containing the blinking molecules, we can't use traditional denoising methods.
- Because the noise in SMLM images is predominantly Poisson, we also can't use the most recent self-supervised denoising models which assume a Gaussian noise model

Abstract:

We evaluate the ability of self-supervised deep learning for Poisson denoising of Single-Molecule Localization Microscopy (SMLM) in addition to the impact denoising can have on the ability to locate molecules within the Single-Molecule Localization Microscopy images. SMLM images are predominantly corrupted with Poisson noise. There is a need for a superior technique to provide accurate SMLM images in order for scientists to gain a better understanding of the functions of live cells at the nanoscale. By denoising SMLM images prior to the images undergoing the current state- of-the-art super-resolution techniques, we create a less corrupted version of SMLM images. As a result, the exact locations of the molecules in the images can be determined with more accuracy and precision. We denoise SMLM images utilizing only the original noisy images as training data with a Self-Supervised Deep Learning model. By modifying the previous Self-Supervised techniques that have been successful in denoising images with Gaussian noise, we remove Poisson noise from SMLM images.

Research Questions:

How well can self-supervised learning denoise SMLM images?

- In comparison with current supervised and self-supervised models

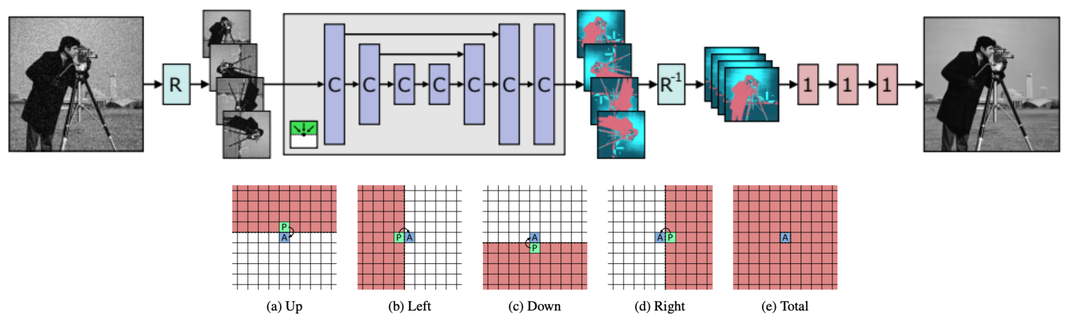
Does denoising SMLM images prior to super-resolution improve the ability to locate molecules?

- In comparison with using just the current ThunderSTORM super-resolution image processing

Model:

Blindspot Model:

The Convolutional Neural Network used for our model is adapted from a group from NVIDIA. The network allows for the true signal of each individual pixel in the noisy image to be learned by obscuring it and taking data from all other pixels. It is an improvement on the most recent self-supervising networks because it allows for the entirety of the image (other than the blinded pixel) to contribute to the loss function.



Loss Function:

To combat the Poisson Noise in our images, we create a loss function that can learn to minimize this type of noise. To do this, we use the conjugate prior, the gamma distribution, to marginalize out the unknown clean values in the probability mass function. From here we calculated the negative log likelihood loss function to train our network:

$$L_i = -\alpha\log(\beta) + (\alpha+z_i)\log(1+\beta) - \log(\Gamma(\alpha+z_i)) + \log(\Gamma(\alpha)) + \log(\Gamma(z_i+1))$$

Gamma Posterior Mean:

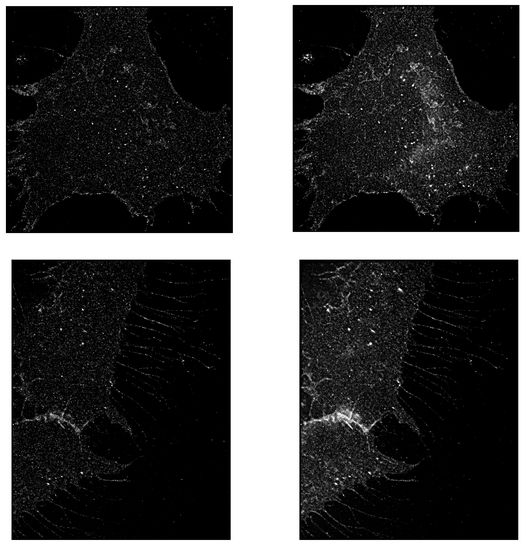
To incorporate the value of the single masked noisy pixel we used the Gamma Posterior mean after training our model to output the clean images. The Gamma Posterior Mean gave better results than the MAP estimation which tended to favor the noisy pixel.

$$x_i = \frac{(\alpha + z_i)}{(\beta + 1)}$$

Results:

Compiled Image Comparisons YFP datasets:

Noisy Molecules: Denoised Molecules:



Pertinent Data:

	Molecules Located	Mean Sigma [nm]	Standard Dev. Sigma [nm]	Mean Uncertainty [nm]	Standard Dev. Uncertainty [nm]
Noisy YFP-Dataset 3	364,509	104.8981	62.35194	17.43365	5.770702
Denoised YFP Dataset 3	882,188	111.466	60.64917	13.46961	6.124521

	Molecules Located	Mean Sigma [nm]	Standard Dev Sigma [nm]	Mean Uncertainty [nm]	Standard Dev. Uncertainty [nm]
Noisy YFT-Dataset 4	153,061	109.2096	88.81490	17.08962	6.1981
Denoised YFT Dataset 4	974,163	138.2151	101.79013	16.90503	5.87431

Simulated Data:

The results for the simulated data also showed visual improvement in denoising and gave a benchmark for comparing the localizations of molecules with a ground truth molecule location for a range of noise levels as well as density masks developed from the YFP datasets. All of the model's output denoised data images obtained a higher Jaccard Indexes than the corresponding simulated data.

Conclusion:

- SMLM are highly corrupted with Poisson noise with no possible ground truth image.
- We developed a self-supervised method for denoising SMLM images.
- The model's outputs visually appeared less noisy. The output is able to locate more molecules than raw images .
- When testing the same models on simulated data, the output's localizations corresponded more accurately to the ground truth than the noisy simulated data's localizations.