

# Single molecule localization microscopy

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## sCMOS noise model

The Poisson rate parameter for a single pixel is

$$\mu_k = \eta \Delta t (N_0 \lambda_k + B_0)$$

where  $\Delta t$  is the camera exposure time and  $N_0$  and  $B_0$  are the fluorophore and background emission rates respectively.

$$\lambda_k = \int_{\text{pixel}} G(x, y) dx dy$$

where the 2D function  $G(x, y)$  is a normalized Gaussian density over the pixel array

$$G(x, y) = \frac{1}{2\pi\sigma^2} e^{-\frac{(x-x_0)^2 + (y-y_0)^2}{2\sigma^2}}$$

## How to compute $\lambda_k$ at each pixel

We can replace this integral with error functions:

$$\lambda_x(x) = \frac{1}{2} \left( \operatorname{erf} \left( \frac{x + a/2 - x_0}{\sqrt{2}\sigma} \right) - \operatorname{erf} \left( \frac{x - a/2 - x_0}{\sqrt{2}\sigma} \right) \right)$$

$$\lambda_y(y) = \frac{1}{2} \left( \operatorname{erf} \left( \frac{y + a/2 - y_0}{\sqrt{2}\sigma} \right) - \operatorname{erf} \left( \frac{y - y/2 - y_0}{\sqrt{2}\sigma} \right) \right)$$

$$\lambda_k(x, y) = \lambda_x(x)\lambda_y(y)$$

The *true signal* is then

$$\vec{S} = [\operatorname{Poisson}(\lambda_1), \operatorname{Poisson}(\lambda_2), \dots, \operatorname{Poisson}(\lambda_N)]$$

## Poisson approximation of pixel values

However, due to readout noise, we measure

$$\vec{H} = \vec{S} + \vec{\xi}$$

The distribution of  $H_k$  is the convolution:

$$\begin{aligned} P(H_k|\theta) &= P(S_k) \circledast P(\xi_k) \\ &= A \sum_{q=0}^{\infty} \frac{1}{q!} e^{-\mu_k} \mu_k^q \frac{1}{\sqrt{2\pi}\sigma_k} e^{-\frac{(H_k - g_k q - o_k)^2}{2\sigma_k^2}} \end{aligned}$$

where  $P(\xi_k) = \mathcal{N}(o_k, \sigma_k^2)$  and  $P(S_k) = \text{Poisson}(g_k \mu_k)$ . In practice, this expression is difficult to work with, so we look for an approximation. Notice that

$$\xi_k - o_k + \sigma_k^2 \sim \mathcal{N}(\sigma_k^2, \sigma_k^2) \approx \text{Poisson}(\sigma_k^2)$$

## The model log likelihood and Hessian matrix

Since  $H_k = S_k + \xi_k$ , we transform  $H'_k = H_k - o_k + \sigma_k^2$ , which is distributed according to

$$H'_k \sim \text{Poisson}(\mu'_k) \quad \mu'_k = g_k \mu_k + \sigma_k^2$$

Since each Poisson r.v. is independent, the negative log likelihood reads

$$\begin{aligned} \ell(\vec{H}) &= -\log \prod_k \frac{e^{-(\mu'_k)} (\mu'_k)^{n_k}}{n_k!} \\ &= \sum_k \log n_k! + \mu'_k - n_k \log (\mu'_k) \end{aligned}$$

## The model log likelihood and Hessian matrix

Fortunately, we can compute the Hessian of the negative log likelihood using the chain-rule for Hessian matrices.

$$\hat{H}_{(\ell,\theta)} = \hat{J}_{(\lambda,\theta)}^T \hat{H}_{(\ell,\lambda)} \hat{J}_{(\lambda,\theta)} + (J_{(\ell,\lambda)} \otimes I_n) \hat{H}_{(\lambda,\theta)}$$

By calculating  $\hat{H}_{(\ell,\theta)}$  at  $\theta_{\text{MLE}}$ , we can get an estimate of the observed information matrix. To do that  $J_{(\lambda,\theta)}$  and  $H_{(\lambda,\theta)}$  are best left to symbolic calculators.

## Localization using a deep generative model

Define particle coordinates as a latent variable  $\mathbf{z}$ . Variational autoencoders use neural networks to represent  $P_{\Theta}(\mathbf{z}|\mathbf{h})$  and  $P_{\Phi}(\mathbf{h}|\mathbf{z})$ .

$$\begin{aligned}D_{\text{KL}}(q(\theta)||p(\theta|x)) &= \mathbb{E}_{\theta \sim q(\theta)} \left( \log \frac{q(\theta)}{p(\theta|x)} \right) \\&= \mathbb{E}_{\theta \sim q(\theta)} \left( \log \frac{q(\theta)p(x)}{p(\theta, x)} \right) \\&= \log p(x) + \mathbb{E}_{\theta \sim q(\theta)} \left( \log \frac{q(\theta)}{p(x|\theta)p(\theta)} \right) \\&= \log p(x) + \mathbb{E}_{\theta \sim q(\theta)} (\log q(\theta) - \log p(x|\theta) - \log p(\theta)) \\&= \log p(x) + H(q) - \mathbb{E}_{\theta \sim q(\theta)} (\log p(x|\theta) + \log p(\theta))\end{aligned}$$