Single molecule localization microscopy

Clayton W. Seitz

April 3, 2023

sCMOS noise model

The Poisson rate parameter for a single pixel is

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

where Δt 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

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

How to compute λ_k at each pixel

We can replace this integral with error functions:

$$\lambda_x(x) = \frac{1}{2}\left(\mathrm{erf}\left(\frac{x + a/2 - x_0}{\sqrt{2}\sigma}\right) - \mathrm{erf}\left(\frac{x - a/2 - x_0}{\sqrt{2}\sigma}\right)\right)$$
$$\lambda_y(y) = \frac{1}{2}\left(\mathrm{erf}\left(\frac{y + a/2 - y_0}{\sqrt{2}\sigma}\right) - \mathrm{erf}\left(\frac{y - y/2 - y_0}{\sqrt{2}\sigma}\right)\right)$$

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

The *true signal* is then

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

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:

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

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

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

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

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

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

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

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.

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

By calculating $\hat{H}_{(l,\theta)}$ at θ_{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 $\boldsymbol{z}$. Variational autoencoders use neural networks to represent $P_{\Theta}(z|h)$ and $P_{\Phi}(h|z)$.

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