Bounding parameter uncertainty in single molecule localization

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June 22, 2022

Photon statistics of CMOS cameras

- Imaging noise consists of shot noise, thermal noise, and readout noise
- Shot noise is Poisson, thermal noise and readout noise are Gaussian

We will adopt the Gaussian PSF approximation (image function):

$$q(x, y) = \frac{1}{2\pi\sigma^2} \exp\left(-\frac{x^2 + y^2}{2\sigma^2}\right)$$

and define the number of photoelectrons at a pixel k as a sum of three random variables

$$H_{\theta,k} = S_{\theta,k} + B_{\theta,k} + W_{\theta,k}$$

where $S_{\theta,k}$ and $B_{\theta,k}$ are Poisson processes for signal and background while $W_{\theta,k}$ represents dark noise of a CMOS array

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The mean values of the signal and background processes are

$$\mu_{\theta,k} = \int_{t_0}^{t} \Lambda(\tau) \int_{C_k} q(x,y)dxdyd\tau$$

$$\beta_{\theta,k} = \int_{t_0}^{t} \Lambda(\tau) \int_{C_k} b(x,y)dxdyd\tau$$

where $b(x,y)$ is a spatially dependent background function. $\Lambda(\tau)$ is the emission rate as a function of time (for example exponential decay for photobleaching).
If we take the dark noise to be Gaussian with mean $m_{\theta,k}$, then we have:

$$\nu_{\theta,k} = \mu_{\theta,k} + \beta_{\theta,k} + m_{\theta,k}$$

We now need to show the form of $P(H_k)$

Monte Carlo integration over a pixel

Computing the mean value at a pixel involves computing an integral $\int_{C_k} q(x, y)dxdy$. This integral is difficult to compute, but a 2D image is really just a 2D histogram. So if we can find the PSF $q(x, y)$ from the objective lens, we can use Monte Carlo integration (sample from the normalized PSF) and multiply by the emission rate ν to compute the mean of the Poisson process at a pixel k

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Let's start by explicitly writing $P(S_k)$

For a CMOS pixel k, the true signal S_k $[\mathrm{ADU}]$ is a Poisson process with rate parameter Λ_k

$$S_k = \gamma g_k P_k(s_k|\Lambda_k)$$

where γ $[e^-/p]$ is the quantum efficiency and g_n $[\mathrm{ADU}/e^-]$ is the pixel's gain

$$P(S_k) = \frac{\exp\left(-\Lambda_k\right)\lambda_k^p}{p!}$$

We can use this to find the distribution over the corrupted signal $P(H_k)$

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To find $P(H_k)$, we first evaluate the joint density $P(S_k, H_k)$

$$
\begin{aligned}
P(S_k, H_k) &= P(H_k|S_k = s)P(S_k = s) \\
&= \frac{1}{Z}\exp\left(-\frac{(H_k - g_k s - \mu_k)^2}{\sigma_k^2}\right)\frac{\exp\left(-\Lambda_k\right)\Lambda_k^s}{s!}
\end{aligned}
$$

Marginalizing over S_k gives the desired distribution over H_n

$$
P(H_k) = \frac{1}{Z}\sum_{s=0}^{\infty}\frac{\exp\left(-\Lambda_k\right)\Lambda_k^s}{s!}\exp\left(-\frac{(H_k - g_k s - \mu_k)^2}{\sigma_k^2}\right)
$$

Fisher Information

Consider the general prescripton of maxmimum likelihood parameter estimation:

$$\mathcal{E}_{\mathrm{MLE}} : \theta^* = \underset{\theta}{\operatorname{argmax}}\, \ell(\mathcal{D}|\theta)$$

where $\ell = \log \mathcal{L}$ is the log-likelihood function

Question: can we derive a theoretical lower bound on our uncertainty in θ^* for an arbitrary estimator $\mathcal{E}$?

Start by defining the *score* of ℓ with respect to θ as

$$\mathcal{S} = \underset{x \sim p}{\mathbb{E}} \left[\frac{\partial}{\partial \theta} \ell(x|\theta) \right]$$

Since x is a continuous random variable, we have to consider the average score

Fisher Information

The Fisher Information $I(\theta)$ is defined as the variance of the score

$$I(\theta) = \mathop{\mathbb{E}}_{x\sim p}\left[\frac{\partial}{\partial\theta}\left(\ell(x|\theta)\right)\right]^2 = \mathop{\mathbb{E}}_{x\sim p}\left[\frac{\partial^2}{\partial\theta^2}\left(\ell(x|\theta)\right)\right]$$

for $x \in \mathcal{D}$. The variance takes this from because it can be shown that $\mathcal{S} = 0$

Intuitively, if the likelihood is insensitive changes in θ, then $\mathcal{D}$ does not provide very much information about θ

When there are many parameters, the Fisher Information (second moment of the score) is a covariance matrix

$$I_{ij}(\theta) = \mathop{\mathbb{E}}_{x\sim p}\left[\frac{\partial}{\partial\theta_i}\left(\ell(x|\theta)\right)\frac{\partial}{\partial\theta_j}\left(\ell(x|\theta)\right)\right]$$

Fisher Information for a multiple parameters

We have shown that the model for the number of photoelectrons at a pixel is

$$P(H_k) = \frac{1}{Z}\sum_{s=0}^{\infty}\frac{\exp\left(-\Lambda_k\right)\Lambda_k^s}{s!}\exp\left(-\frac{(H_k - g_k s - \nu_k)^2}{\sigma_k^2}\right)$$

Notice that ν_k is dependent on $\int q(x,y)dxdy$ and therefore the PSF parameters $\theta = (\mu_x, \mu_y, \sigma)$. These can be plugged into the following Fisher information matrix

$$\begin{aligned} I_{ij}(\theta) &= \mathop{\mathbb{E}}_{H\sim P}\left[\frac{\partial}{\partial\theta_i}\left(\log\prod_k P(H_k)\right)\frac{\partial}{\partial\theta_j}\left(\log\prod_k P(H_k)\right)\right] \\ &= \mathop{\mathbb{E}}_{H\sim P}\sum_k\left[\frac{\partial}{\partial\theta_i}\log P(H_k)\frac{\partial}{\partial\theta_j}\log P(H_k)\right] \end{aligned}$$

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