Detecting neuronal activity from calcium imaging data using FRI methods

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Motivation

- Information is sent between neurons by action potentials (‘spikes’).
- The goal of many experiments is to monitor a neuron’s spiking activity, written mathematically as a stream of Diracs: \( x(t) = \sum_{k=1}^{K} \delta(t - t_k) \).
Calcium imaging: functional imaging of neural activity

- Spiking activity is visualized by a fluorescent indicator, which causes a neuron to emit a pulse of fluorescence with a characteristic shape, $p(t)$, when a spike is fired.

- The signal from one neuron over time, $f(t)$, is thus modelled as $f(t) = x(t) * p(t)$:

\[
x(t) = \sum_{k=1}^{K} a_k \delta(t - t_k) \quad \text{and} \quad p(t) = (e^{-\alpha t} - e^{-\gamma t}) 1_{t \geq 0}
\]
Advantages of calcium imaging

- Can monitor activity of 100s - 1000s of neurons simultaneously, at single cell resolution.
- Can image *in vivo* in behaving animals.
- Can image same cell populations over multiple months.

**BUT the datasets present a challenging signal processing problem.**

Detecting neuronal activity from calcium imaging data
Estimating the boundary of an isolated cell

- We aim to partition the local region into two subregions: the cell ($\Omega^{\text{in}}$) and the background ($\Omega^{\text{out}}$).
- Starting with an initial estimate of $\Omega^{\text{in}}$ and $\Omega^{\text{out}}$, we use the average signal from the respective subregions ($f^{\text{in}}$ and $f^{\text{out}}$) as a feature with which to classify pixels into cell interior or background.
- We compare the temporal activity at pixel $x = (x_1, x_2)$, $I(x) \in \mathbb{R}^N$, with the average subregion time courses.
Cost function for isolated cell

We define the optimal partition as the one that minimises the following cost function:

$$E_{\text{ext}}(\Omega^\text{in}, \Omega^\text{out}) = \int_{\Omega^\text{in}} D(I(x), f^\text{in}) \, dx + \int_{\Omega^\text{out}} D(I(x), f^\text{out}) \, dx,$$

(1)

where \( D \) is a non-negative dissimilarity metric that is zero when the two arguments are identical.

Depending on the fluorescent indicator, for the dissimilarity metric we use either the Euclidean distance or correlation:

$$D(I(x), f) = \| I(x) - f \|^2 \quad \text{or} \quad D(I(x), f) = 1 - \text{corr}(I(x), f).$$

(2)
Evolve contour to decrease cost function

- Starting from an initial estimate, the cell boundary evolves to minimise the cost function.
- The contour evolves with respect to an artificial time parameter $\tau$.

- We implicitly represent the evolving boundary estimate by a Level Set function, $\phi(\tau)$.
- $\phi(\tau)$ evolves to minimize $\mathcal{E}$, which is the sum of the cost function introduced earlier and a regularizer: $\mathcal{E} = \mathcal{E}_{\text{ext}} + \mathcal{R}$. 

$\phi(0)$
Evolving the contour estimate using level set method

We find the level set function that is the steady state solution of the gradient flow equation

$$\frac{\partial \phi}{\partial \tau} = -\frac{\partial \mathcal{E}}{\partial \phi}. \tag{1}$$

The velocity from the data-based cost function is:

$$\frac{\partial \mathcal{E}_{\text{ext}}}{\partial \phi} = V(x)\delta_{\epsilon}(x) \quad \text{and} \quad V(x) = D(I(x), f^{\text{in}}) - D(I(x), f^{\text{out}}). \tag{2}$$
Extension to multiple regions

When we have multiple cells with interiors $\{\Omega^{\text{in},1}, \Omega^{\text{in},2}, ..., \Omega^{\text{in},M}\}$ and a global exterior $\Omega^{\text{out}}$, the cost function is

$$\mathcal{E}_{\text{ext}}(\Omega^{\text{in},1}, ..., \Omega^{\text{in},M}, \Omega^{\text{out}}) = \int_{\Omega^{\text{out}}} D(I(x), f^{\text{out}}) \, dx + \int_{\text{inside}} D(I(x), \sum_{i \in C(x)} f^{\text{in},i}) \, dx. \quad (1)$$

- We evolve one function $\phi_i$ for each cell interior.
- When cells are sufficiently separate they can be evolved independently.
Results on in vivo imaging data

Detecting neuronal activity

**GOAL:** Infer a neuron’s spike train $x(t)$ from the fluorescence signal $f(t)$.

$$ f_{\alpha,\gamma}(t) = x(t) = \sum_{k=1}^{K} a_k \delta(t - t_k) \quad p(t) = (e^{-\alpha t} - e^{-\gamma t})_{t \geq 0} $$

- The parameters $\alpha$ and $\gamma$ are known and depend on the fluorescent indicator.
- The unknown parameter set to be estimated is $\{a_k, t_k\}_{k=1}^{K}$.
- $f(t)$ is a signal with Finite Rate of Innovation.
FRI spike detection method

We identify a mapping from $f(t)$ to samples of the Fourier Transform of the spike train $\hat{x}(\omega)$:

$$\left\{ \hat{x}(\omega_m^T) \right\}_{m=0}^P$$

where $T$ is the sampling period of $f(t)$ and the frequencies $\omega_m$ are design parameters. The mapping depends on the pulse shape:

$$p(t) = e^{-\alpha t} \mathbf{1}_{t \geq 0} \quad [1]$$

$$p(t) = (e^{-\alpha t} - e^{-\gamma t}) \mathbf{1}_{t \geq 0} \quad [2]$$


Recovering spike times

If the sampling kernel $\psi$ satisfies

$$
\sum_{n \in \mathbb{Z}} c_{m,n} \psi(t - n) = e^{i\omega_m t},
$$

then, taking a linear combination of the samples,

$$
\begin{align*}
    s_m &= \sum_n c_{m,n} w_n \\
    &= \sum_{k=1}^{K} b_k u_k^m = \hat{x}\left(\frac{-\omega_m}{T}\right),
\end{align*}
$$

where $u_k = e^{i\lambda t_k/T}$. There are many methods then to recover $t_k$ from $s_m$. 

Mapping $f(t)$ to $\hat{x}(\omega)$

We prove that the above operations are equivalent to the samples obtained by filtering $x(t)$ with $\psi$:

$$\psi(t) = \varphi(t) * \beta_{-\alpha T}(-t) * \beta_{-\gamma T}(-t).$$

$$w_n = \langle x(t), \psi\left(\frac{t}{T} - n\right) \rangle$$
Spike detection results on real data

Average results on real in vivo mouse visual cortex data (total length 678s, 532 spikes). We compare against Vogelstein et al.’s deconvolution algorithm [1].

We detect 90% of spikes within 0.033s of the true location.

Conclusion

- Multi-photon calcium imaging is a promising tool for monitoring neuronal microcircuits at single-cell resolution in behaving animals.
- We have presented a Level Set method to detect the locations of cells in calcium imaging data.
- We have presented an FRI algorithm to detect spikes from the corresponding time courses.
Thanks for listening!

Any questions?