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Detecting neuronal activity from calcium imaging data using FRI methods

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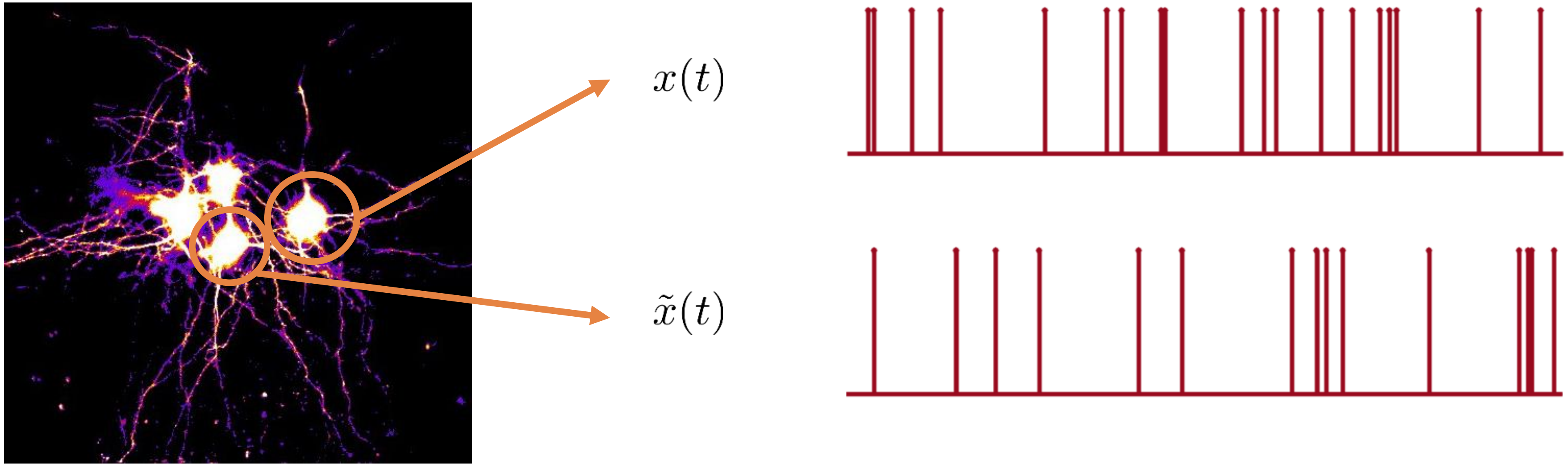
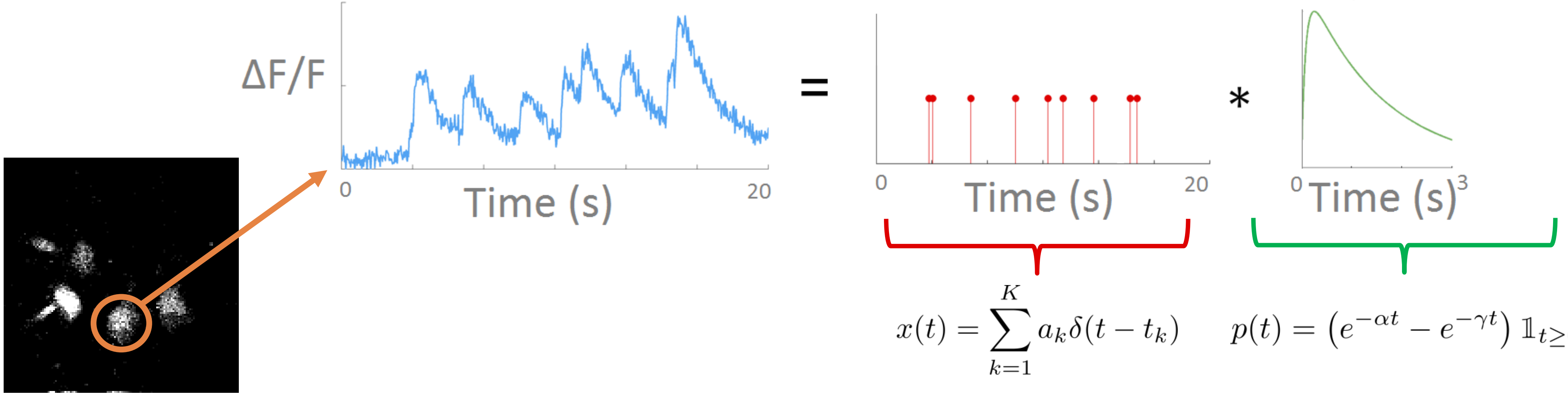
Motivation

- 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: $x(t) = \sum_{k=1}^{K} \delta(t - t_k)$.



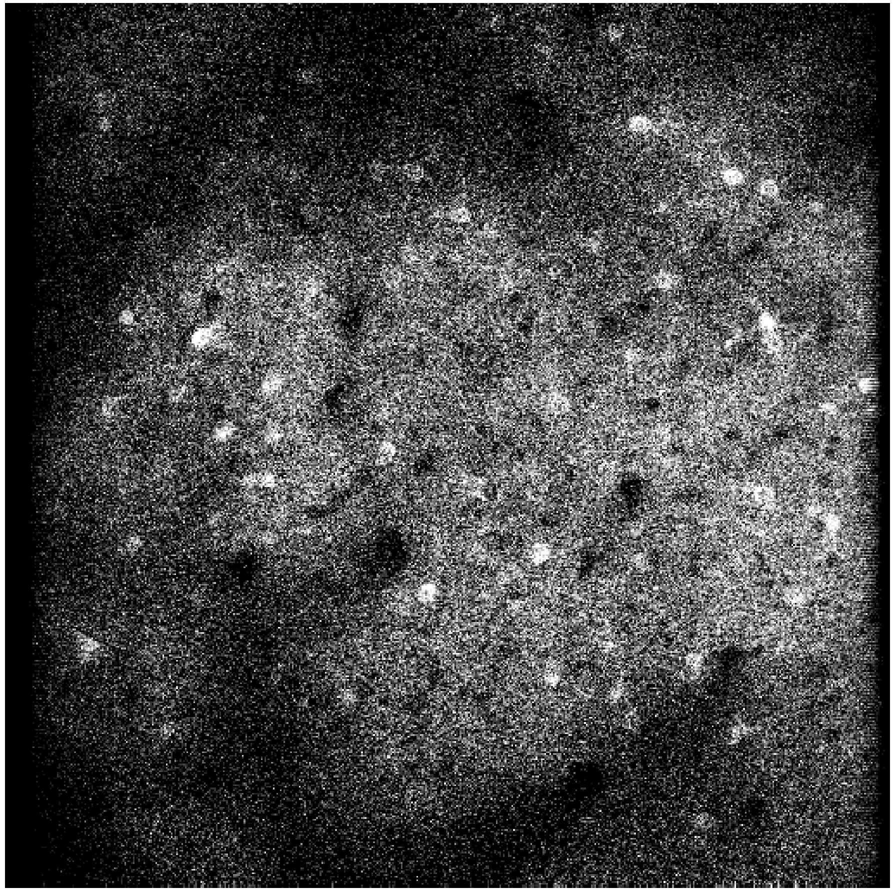
Calcium imaging: functional imaging of neural activity

- 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 $f(t) = x(t) * p(t)$:



$$x(t) = \sum_{k=1}^{K} a_k \delta(t - t_k) \qquad p(t) = \left(e^{-\alpha t} - e^{-\gamma t}\right) \mathbb{1}_{t \geq 0}$$

Advantages of calcium imaging

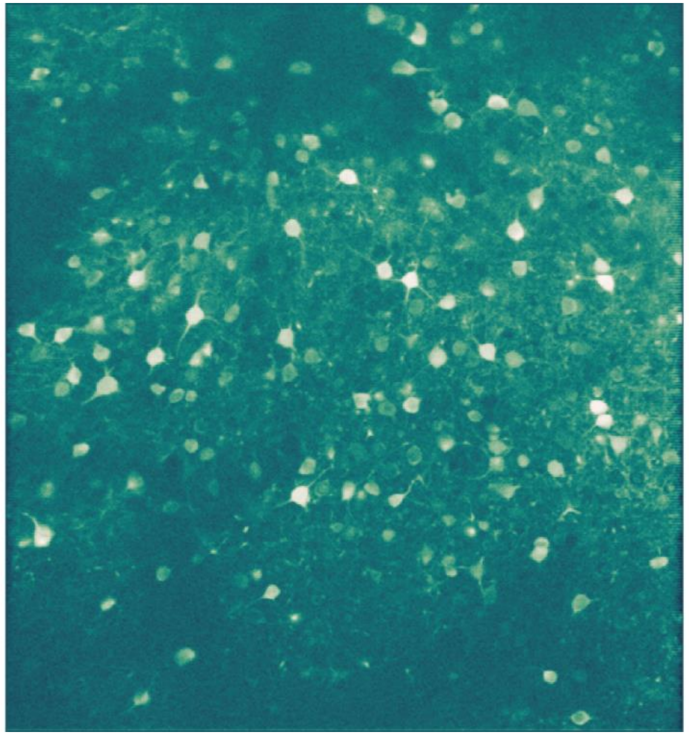


- Can monitor activity of 100s - 1000s of neurons simultaneously, at single cell resolution.
- Can image *in vivo* in behaving animals.
- Can image same cell populations over multiple months.

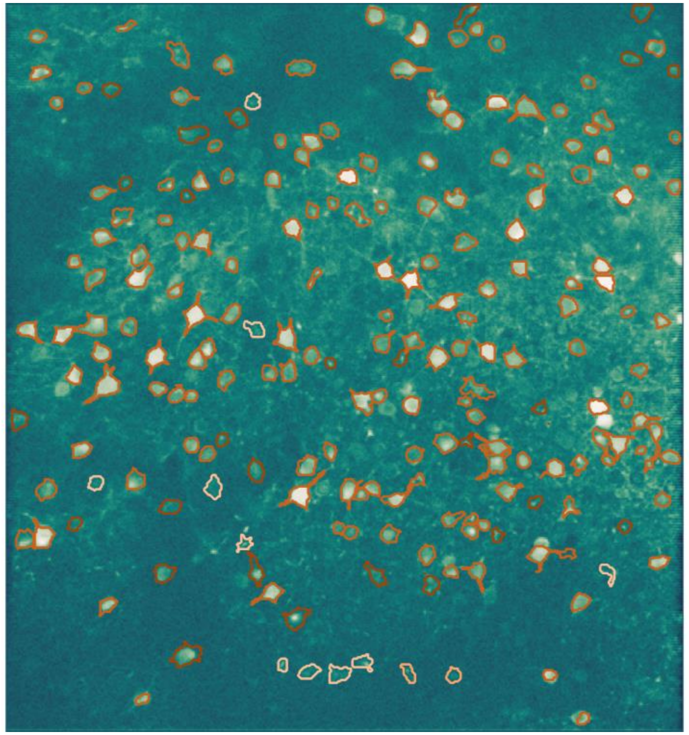
BUT the datasets present a challenging signal processing problem.

[1] Dataset available online: http://neurofinder.codeneuro.org/. Accessed 01/07/2017.

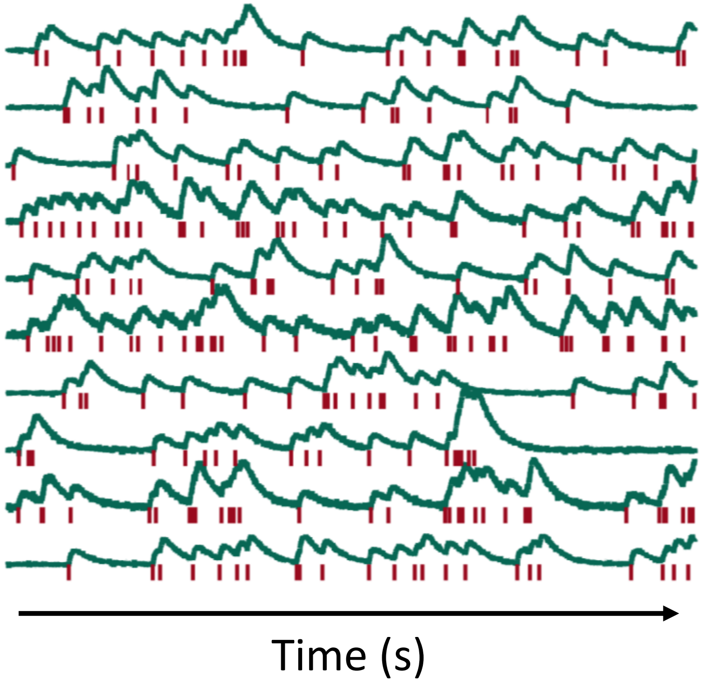
Detecting neuronal activity from calcium imaging data



DETECT CELL LOCATIONS

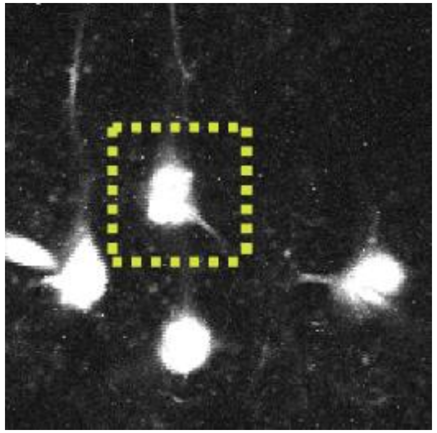


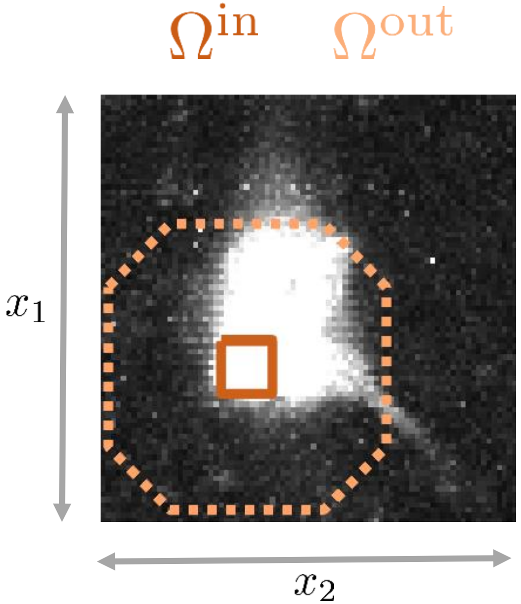
DETECT SPIKES

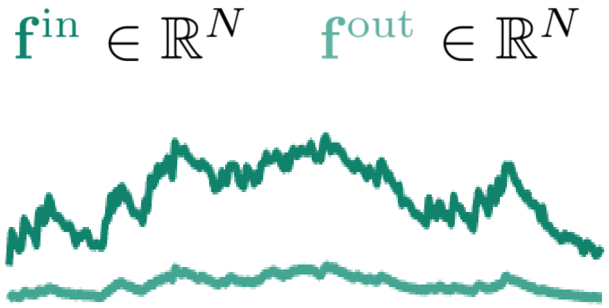


Estimating the boundary of an isolated cell

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







Cost function for isolated cell

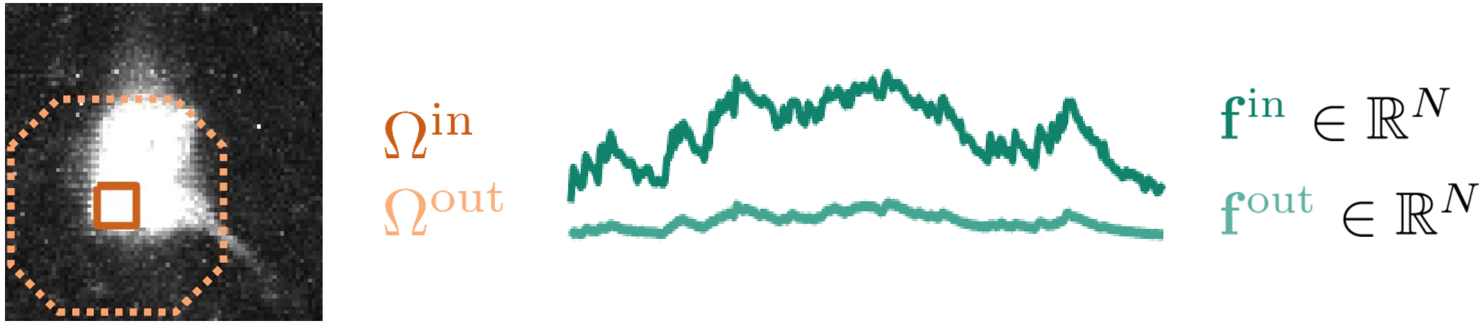
We define the optimal partition as the one that minimises the following cost function:

$$\mathcal{E}_{\text{ext}}(\Omega^{\text{in}}, \Omega^{\text{out}}) = \int_{\Omega^{\text{in}}} D\Big(\mathbf{I}(\mathbf{x}),\ \mathbf{f}^{\text{in}}\Big)\,\mathrm{d}\mathbf{x} + \int_{\Omega^{\text{out}}} D\Big(\mathbf{I}(\mathbf{x}),\ \mathbf{f}^{\text{out}}\Big)\,\mathrm{d}\mathbf{x}, \tag{1}$$

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

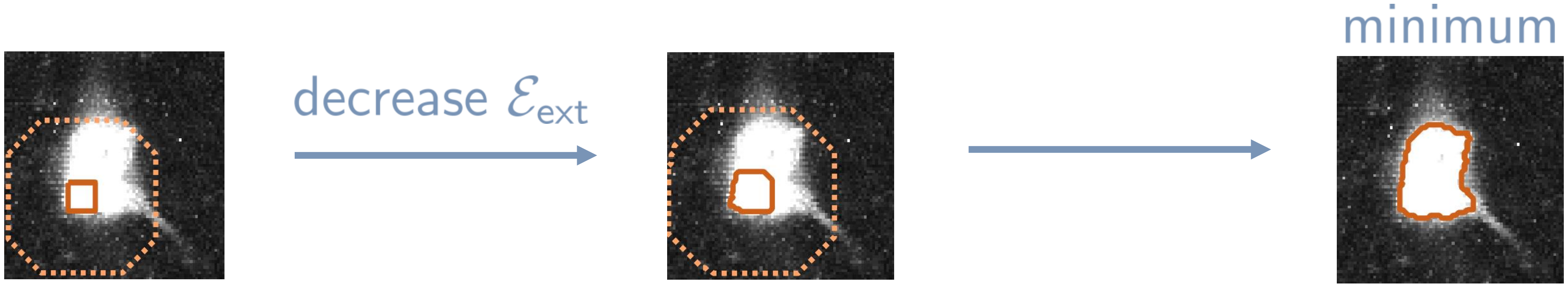
Depending on the fluorescent indicator, for the dissimilarity metric we use either the Euclidean distance or correlation:

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

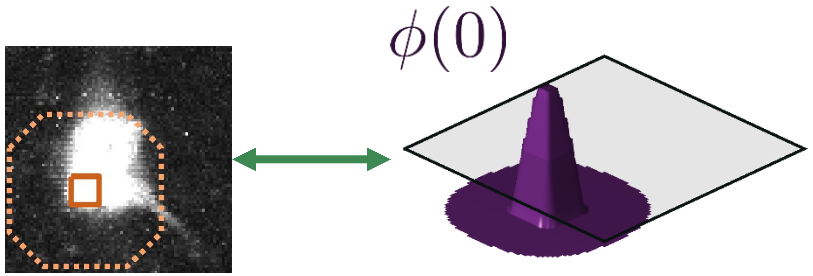

Ω^{in}
Ω^{out}
$\mathbf{f}^{\text{in}} \in \mathbb{R}^N$
$\mathbf{f}^{\text{out}} \in \mathbb{R}^N$

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 artifical time parameter τ.



- 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: $\mathcal{E} = \mathcal{E}_{\text{ext}} + \mathcal{R}$.



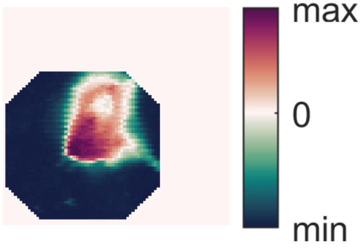
Evolving the contour estimate using level set method

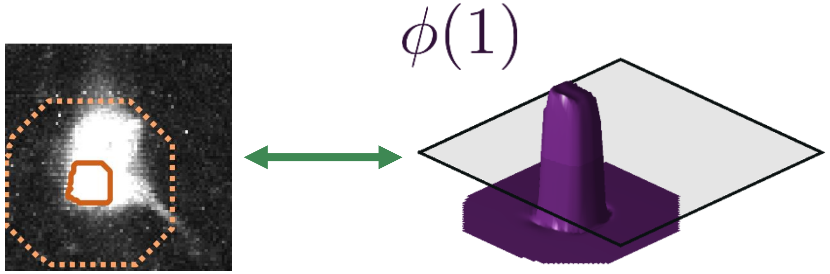
We find the level set function that is the steady state solution of the gradient flow equation

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

The velocity from the data-based cost function is:

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



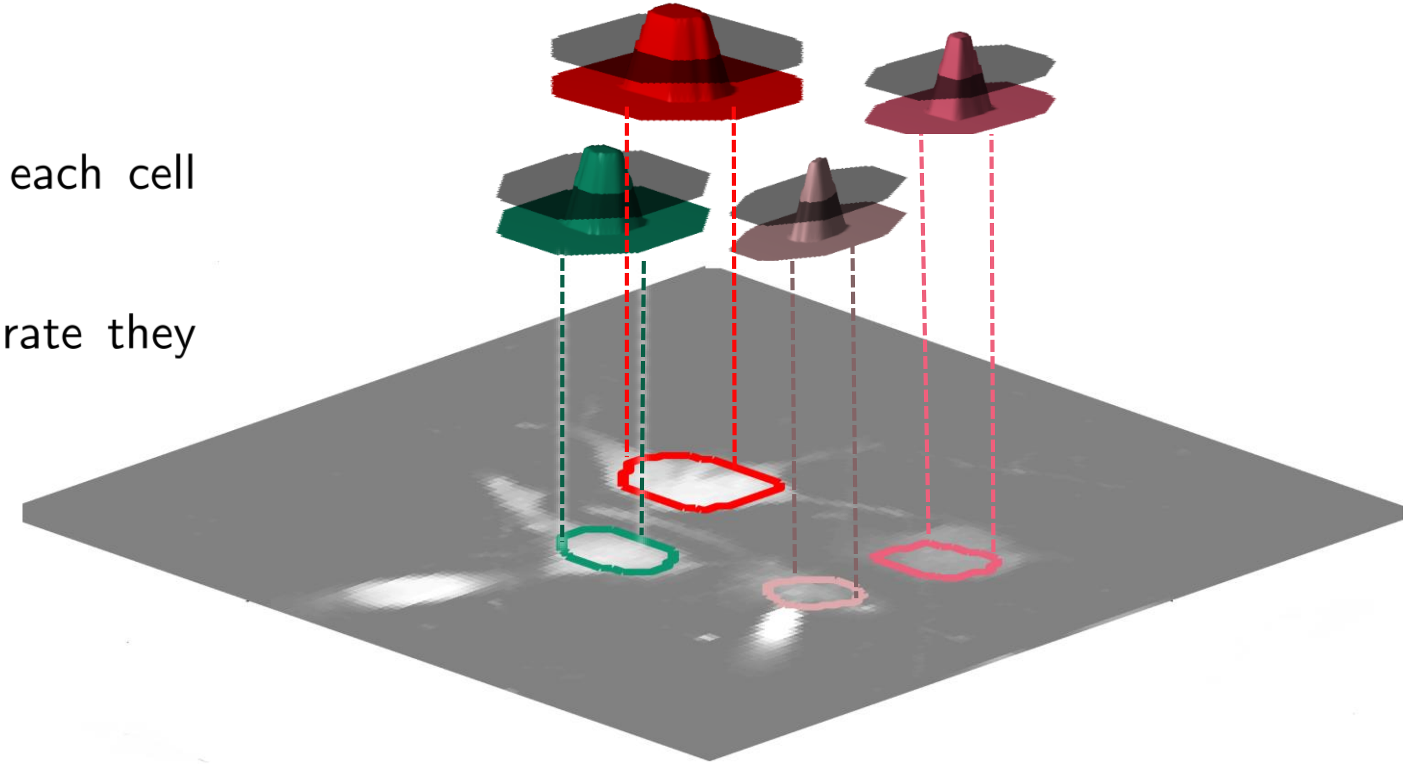


Extension to multiple regions

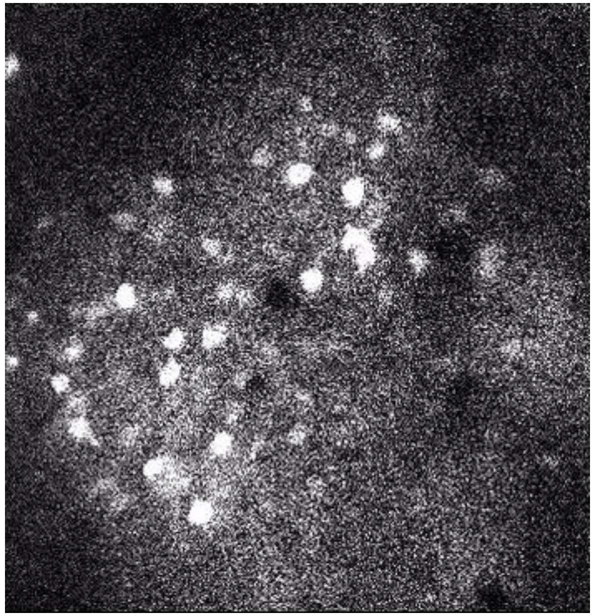
When we have multiple cells with interiors $\{\Omega^{\text{in},1}, \Omega^{\text{in},2}, \ldots, \Omega^{\text{in},M}\}$ and a global exterior Ω^{out}, the cost function is

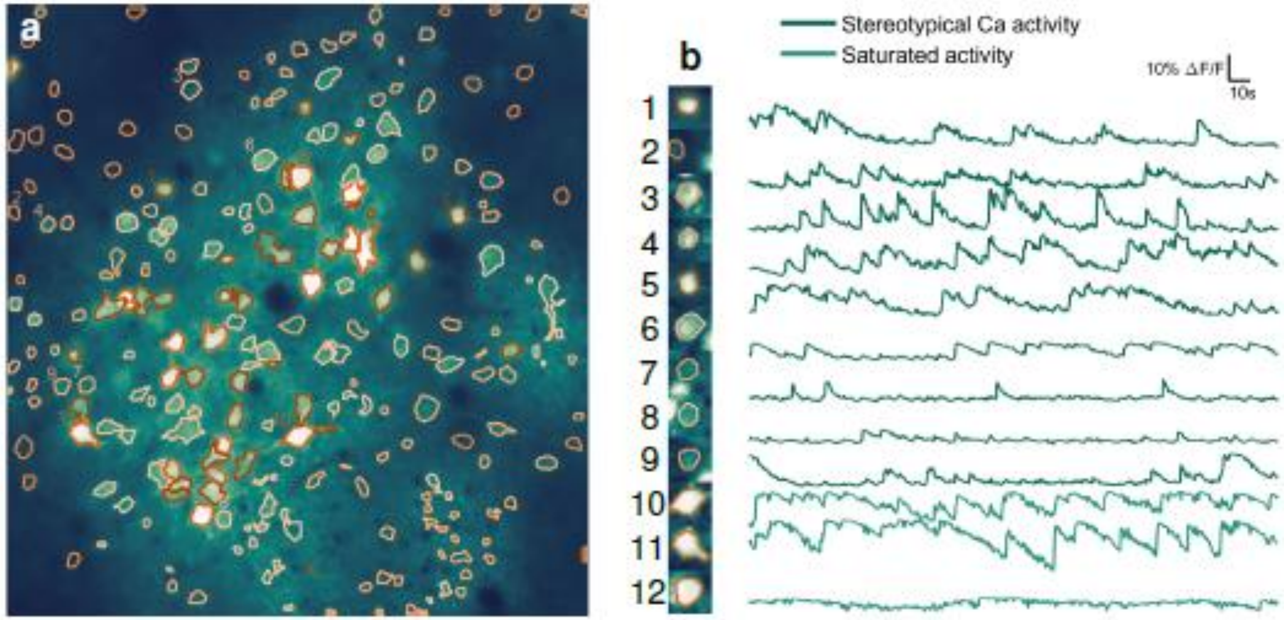
$$\mathcal{E}_{\text{ext}}(\Omega^{\text{in},1}, \ldots, \Omega^{\text{in},M}, \Omega^{\text{out}}) = \int_{\Omega^{\text{out}}} D\Big(I(\mathbf{x}),\ \mathbf{f}^{\text{out}}\Big)\,\mathrm{d}\mathbf{x} + \int_{\text{inside}} D\Big(I(\mathbf{x}),\ \sum_{i \in C(\mathbf{x})} \mathbf{f}^{\text{in},i}\Big)\,\mathrm{d}\mathbf{x}. \tag{1}$$

- We evolve one function ϕ_i for each cell interior.
- When cells are sufficiently separate they can be evolved independently.



Results on in vivo imaging data

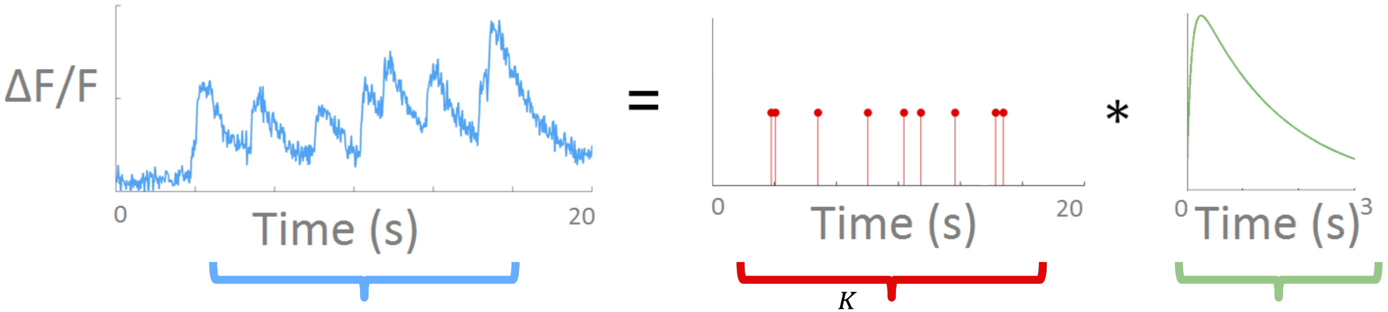




[1] Simon Peron, Jeremy Freeman, Vijay Iyer, Caiying Guo, Karel Svoboda (2015); Volumetric calcium imaging data recorded during performance of a single whisker object localization task, sampling activity in the majority of the relevant superficial barrel cortex neurons (75 %, 12,000 neurons per mouse). CRCNS.org.

Detecting neuronal activity

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

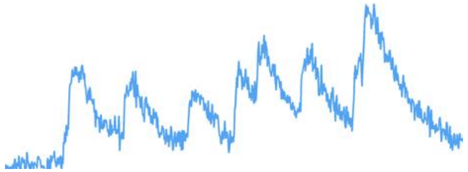


$$f_{\alpha,\gamma}(t) \qquad x(t) = \sum_{k=1}^{K} a_k \delta(t - t_k) \qquad p(t) = (e^{-\alpha t} - e^{-\gamma t})\mathbb{1}_{t\geq 0}$$

- The parameters α and γ 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

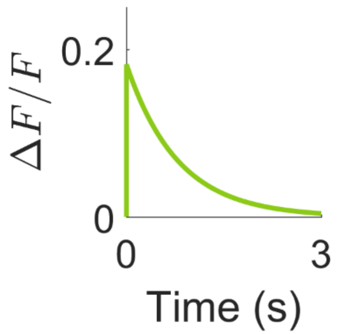
We identify a mapping from $f(t)$ to samples of the Fourier Transform of the spike train $\hat{x}(\omega)$:



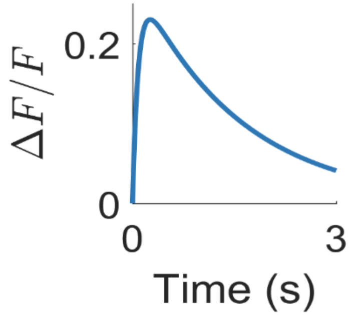
$$\longmapsto \quad \left\{\hat{x}\left(-\frac{\omega_m}{T}\right)\right\}_{m=0}^{P}$$

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

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



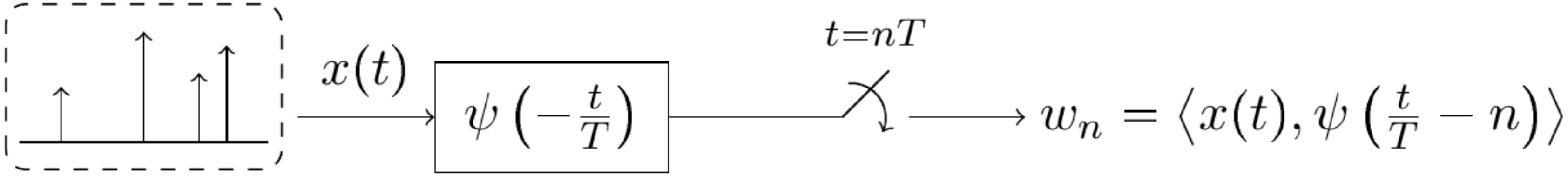
$$p(t) = \left(e^{-\alpha t} - e^{-\gamma t}\right)\mathbb{1}_{t\geq 0} \quad [\mathbf{2}]$$



[1] Õnativia, J et al. (2013). A finite rate of innovation algorithm for fast and accurate spike detection from two-photon calcium imaging. Journal of neural engineering, 10(4), 046017.

[2] Reynolds, S et al. An extension of the FRI framework for calcium transient detection in 2016 IEEE International Symposium on Biomedical Imaging (ISBI).

Recovering spike times


$x(t)$
$\psi\left(-\frac{t}{T}\right)$
$t=nT$
$w_n = \langle x(t), \psi\left(\frac{t}{T}-n\right)\rangle$

If the sampling kernel ψ satisfies

$$\sum_{n\in\mathbb{Z}} c_{m,n}\psi(t-n) = e^{j\omega_m t}, \tag{1}$$

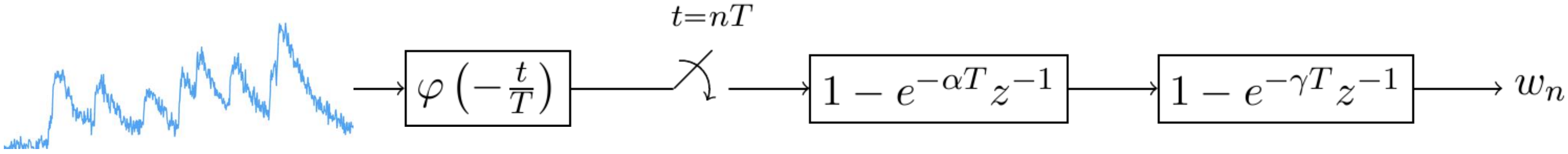
then, taking a linear combination of the samples,

$$s_m = \sum_{n} c_{m,n} w_n \tag{2}$$

$$= \sum_{k=1}^{K} b_k u_k^m = \hat{x}\left(\frac{-\omega_m}{T}\right), \tag{3}$$

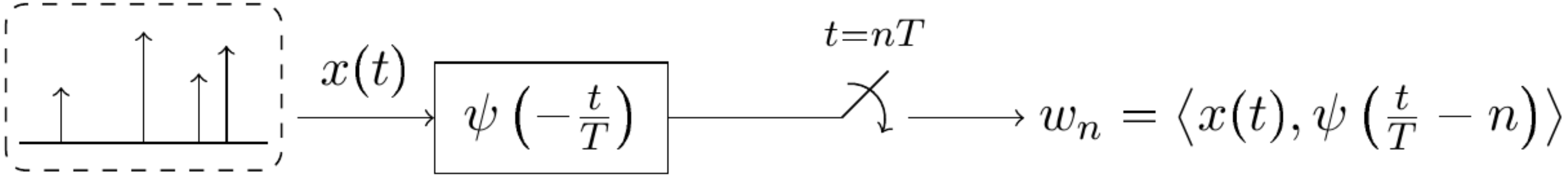
where $u_k = e^{j\lambda t_k/T}$. There are many methods then to recover t_k from s_m.

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

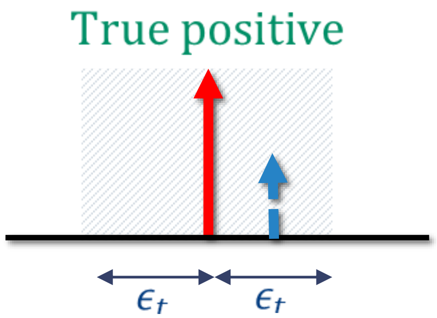


We prove that the above operations are equivalent to the samples obtained by filtering $x(t)$ with ψ:

$$\psi(t)=\varphi(t)*\beta_{-\alpha T}(-t)*\beta_{-\gamma T}(-t). \qquad (1)$$

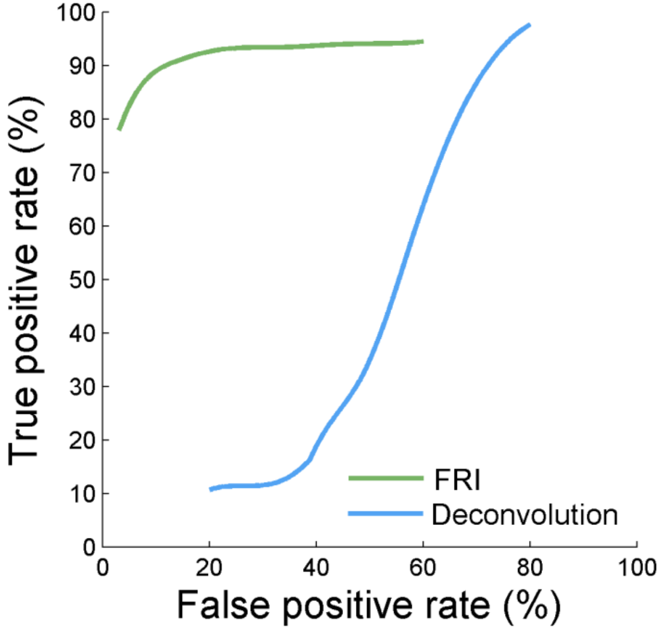

$x(t)$
$\psi\left(-\frac{t}{T}\right)$
$t{=}nT$
$w_n=\langle x(t),\psi\left(\frac{t}{T}-n\right)\rangle$

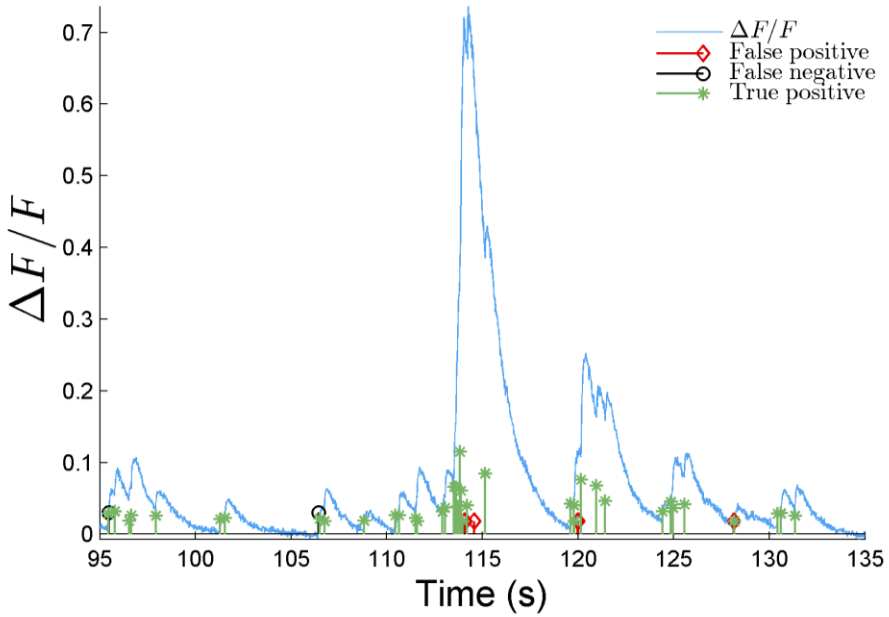
Spike detection results on real data



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.





[1] Vogelstein, J T et al. "Fast nonnegative deconvolution for spike train inference from population calcium imaging." *Journal of neurophysiology* 104.6 (2010): 3691-3704.

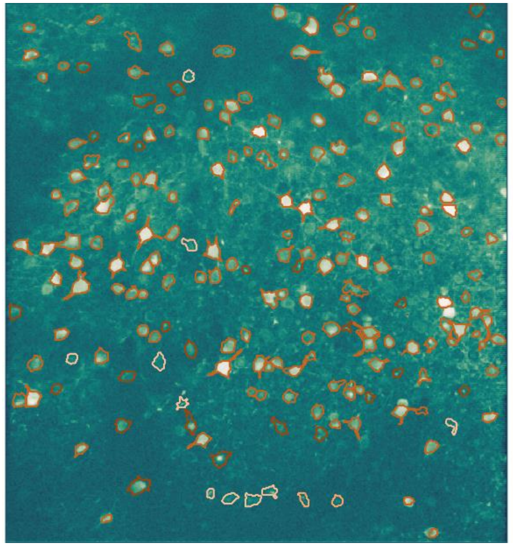
Conclusion

- Multi-photon calcium imaging is a promising tool for **monitoring neuronal microcircuits at single-cell resolution** in behaving animals.

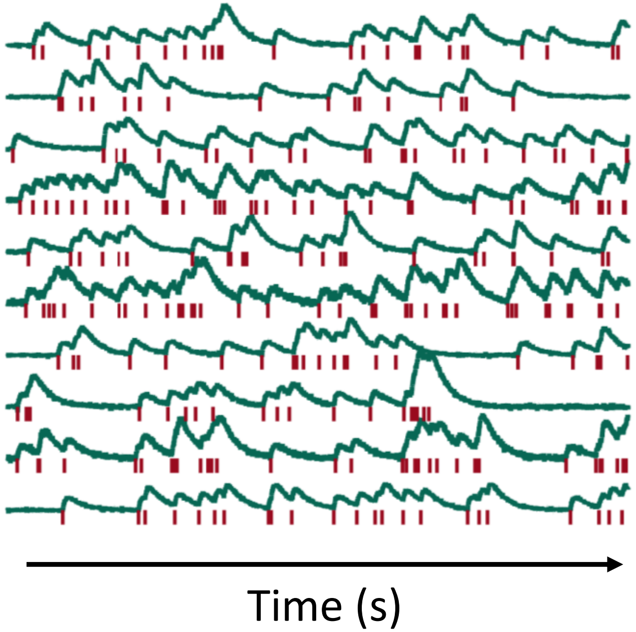
- We have presented a Level Set method to **detect the locations of cells** in calcium imaging data.

- We have presented an **FRI algorithm to detect spikes** from the corresponding time courses.

DETECT CELL LOCATIONS



DETECT SPIKES



Thanks for listening!

Any questions?