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Neural Spikes, Identification from a Multielectrode Array

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Synonyms and Abbreviations

Action potential (Spike); Multi-electrode array (MEA); Ordering points to identify the clustering structure (OPTICS algorithm); Retinal ganglion cell (RGC); Spacetime pixel (Stixel); Spike identification (Spike sorting)

Definitions

The brain and other neural tissue contain many types of cells, notably including *neurons*, cells that are specialized for information processing and communication. The output of most neuron types consists of *spikes*, that is, rapid changes in the electrical potential across their outer membrane. Each spike creates a detectable disturbance in electric potential in the medium surrounding the neuron. *Extracellular recording* of spikes attempts to detect and analyze those disturbances, a task that is complicated by the fact that an extracellular electrode typically picks up signals from many different neurons. Such signals must therefore be decomposed into contributions from each of the underlying neurons, a procedure called *spike sorting*. Unambiguous spike sorting is made easier by the recent availability of large, high-density *multi-electrode arrays* (MEAs) that simultaneously monitor dozens or even thousands of electrodes. This entry describes a class of methods for sorting MEA data based on Bayes's formula ("Bayesian" spike sorting methods).

Overview

The vertebrate retina is a popular model system for neuroscience, in part because it is so amenable to detailed study. Similar recordings can now also be made in other brain areas [2]. However, recordings obtained in this way are useful only if every spike can be correctly assigned to the neuron that generated it (the "spike sorting problem"). Reviews of early work on spike sorting can be found in Lewicki [5] and Quian Quiroga [10].

Spike sorting is possible in principle because each neuron is located at a fixed position relative to each electrode, generating a distinctive pattern of excitation amplitudes on the array of electrodes; also, the amplitude and time course of each neuron's spikes are at least partly similar to each other, and different from those of neighboring neurons. Nevertheless, it is a nontrivial task to determine each of the ideal waveforms

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(the "templates"), separating them from each other and from noise. Moreover, in practice there can be significant variation in the spike waveforms from a given neuron (for instance in amplitude), complicating the task of determining from data which templates are present in a sample. That is, spike sorting is a problem in probabilistic inference.

This entry outlines an algorithm that carries out this program [9], combining elements from several key articles (e.g., [3, 6–8, 11]). Other relevant approaches include [4, 12, 13].

Typical Experiment and Data

All illustrative data were recorded at 10 kHz from albino guinea pig retina, presented with a standard random visual stimulus. Data were taken with a 30-electrode MEA from MultiChannel Systems (MCS GmbH, Reutlingen, Germany), covering about 0.018 mm^2 of retina.

The black curves in Fig. Fig. 1a,b show some representative data, as arrays of graphs each representing a time series of recorded potentials on a particular electrode (or "channel"). In addition to identifiable spikes, each electrode has activity that we will collectively refer to as "noise."

Spike Identification Method

Figure 2 summarizes the steps described below. After data acquisition and high-pass filtering, the data are packaged into two types of 3.2 ms clips: (a) "noise clips," in which the potential never crosses a threshold, and (b) "spike events," each surrounding a moment at which the potential crosses (falls below) −4 times the standard deviation of the potential in the noise clips [11]. A small subset of the spike events was extracted to speed up the analysis steps shown in dashed lines in Fig. Fig. 2.

Clustering and Template Building

Each spike event consists of $N = 3.2\,\text{ms} \times 10\,\text{kHz} \times 5 \times 6 = 960$ numbers, the potentials on a $32 \times 5 \times 6$ grid of spacetime pixels ("stixels"). Each event involves a superposition of spikes drawn from an unknown number of classes corresponding to distinct neurons. The first step is to find those classes, including characterizing each class's mean waveform and its variability. That is, we must *cluster* the spike events.

A powerful algorithm well suited to this task is OPTICS [1]. Strictly speaking, OPTICS does not cluster data; instead, it reorders a given set of points into a single linear sequence in which similar elements are placed close to each other. If a feature such as overall amplitude varies continuously among exemplars, they are grouped together; if that feature is bunched into two or more clusters, they will be visibly separated in the sequence. A human operator can then rapidly scan the ordered list of exemplars and cut it into batches corresponding to distinct clusters [9].

The steps described above produce clusters, that is, collections of similar events ("exemplars" of the cluster). The next step is to create a consensus waveform ("template") summarizing each cluster, and characterize the deviations from that consensus. Figure Fig. 3 shows the result of taking the template to be the pointwise median of the aligned exemplars in a cluster. A particular exemplar may contain other activity besides the spike of interest. Choosing the median prevents such chance collisions from influencing the template, because at any particular stixel most exemplars do *not* display any additional spike.

Individual instances of a particular spike type will deviate from the template. However, at least in guinea pig retina, the most significant sources of variation are (a) additive noise and (b) overall multiplicative rescaling of the spike's amplitude. To quantify (b), for each exemplar the method finds the overall rescaling factor A that optimizes the overlap of that exemplar and the template, then stores the mean and variance of those factors in a lookup table for later use as a prior probability (2). Finally, it logs the number of exemplars in each template, converts to an approximate firing rate, and saves those rates, again for later use as a prior.

In the discussion below, the index μ represents template type; the symbol $F_{\mu;x,y,t}$ refers to the potential of template μ, on the electrode with address x, y, at time t.

Spike Fitting

The preceding steps yield templates of various discrete types, indexed by μ. Within each type, there are also continuous variations in amplitude, which we express as an overall multiplicative factor A relative to the

template; there is also a choice of firing time t_1. A "spike descriptor" is a specification of all these variables. The next stage of spike sorting is to identify what spike(s) are present in each event of the full dataset ("spike fitting"). The strategy is to evaluate the posterior probability of each spike descriptor given that event, marginalize over uninteresting variations within that type (the value of A), then maximize over the remaining variables (μ and t_1).

Generative Model

To obtain the posterior probability, one must find formulas for the prior probability of a spike descriptor, and for the likelihood (probability that a particular waveform would occur if that spike were present). That is, we must specify an explicit generative model of the data [8].

Before writing formulas, we first summarize in words the general assumptions of the generative model. The assumptions are: (1) Each neuron generates spike waveforms that are all identical, apart from overall amplitude scale and additive noise; (2) The signal (spikes) and the noise are statistically independent of each other; (3) The signal and noise sum linearly; (4a) The noise, and (4b) the variability of spike amplitudes, are well described by Gaussian distributions; and (5) The prior probability that each neuron will fire is independent of its, and the others', histories, and of the stimulus.

Assumption (4a) implies that the noise is characterized by a covariance matrix, C. Evaluating C empirically on noise clips shows that: It is approximately diagonal, and translation-invariant, in space; and it is approximately stationary, that is, invariant under time shifts. Moreover, its dependence on time is roughly exponential: $\mathsf{C}(x, y, t; x', y', t') = \eta\delta_{x,x'}\delta_{y,y'}\mathrm{e}^{-|t-t'|/\tau}$. That is, C is determined by just two empirical quantities, the strength η and correlation time τ of the noise. In this formula, $\delta_{x,x'}$ is the Kronecker symbol.

We can now express the content of assumption (4a). We regard x, y, t as a single N-valued index and describe a noise clip by an N-component vector $\mathbf{V}$ of potentials. Then the noise model states that the probability density function for noise samples is $P_{\mathrm{noise}}(\mathbf{V})\mathrm{d}^N\mathbf{V} = (2\pi)^{-N/2}(\det\mathsf{C})^{-1/2}\mathrm{e}^{-\mathbf{V}^{\mathrm{t}}\mathsf{C}^{-1}\mathbf{V}/2}\mathrm{d}^N\mathbf{V}$.

Fitting a Single Spike

Given an event, we wish to know if it contains any spikes, and if so to identify them. First, temporarily suppose that we know that the event contains exactly one spike. We wish to know the spike's type μ and time of occurrence t_1. Our best estimate of these quantities comes from maximizing the posterior probability density $\mathcal{P}(\mu, t_1|\text{event})$, where "event" is the recorded time series of potentials on each electrode. This density is in turn obtained by marginalizing $\mathcal{P}(\mu, t_1, A|\text{event})$ over A, the amplitude scale factor of the spike relative to the template.

Using Bayes's formula, we can obtain $\mathcal{P}$ as a constant times a likelihood times a prior, or

$$\mathcal{P}(\mu, t_1, A|\text{event})\mathrm{d}t_1\mathrm{d}A = KP(\text{event}|\mu, t_1, A)\,P(\mu, t_1, A)\mathrm{d}t_1\mathrm{d}A\,, \quad (1)$$

where K is independent of μ, A, t_1. The differential $\mathrm{d}A\mathrm{d}t_1$ reminds us that $\mathcal{P}$ is a probability density function, with units s^{-1}.

The likelihood function describes the distribution of actual observations given the ideal spike. The assumptions outlined earlier amount to supposing that the observed signal will differ from the rescaled ideal by additive noise, so we simply write the likelihood as $P(\text{event}|\mu, t_1, A) = P_{\mathrm{noise}}(\delta\mathbf{V})$, where $\delta\mathbf{V} = \mathbf{V} - A\mathbf{F}_{\mu,t_1}$. In this formula, the shifted template vector $\mathbf{F}_{\mu,t_1}$ has x, y, t component equal to $F_{\mu;x,y,(t-t_1)}$.

Turning to the prior, assumptions (4b) and (5) give it as

$$P(\mu, t_1, A)\mathrm{d}t_1\mathrm{d}A = \big(r_\mu\mathrm{d}t_1\big)\big((2\pi{\sigma_\mu}^2)^{-1/2}\mathrm{e}^{-(A-\gamma_\mu)^2/2\sigma_\mu^2}\mathrm{d}A\big), \quad (2)$$

where γ_μ is the mean and ${\sigma_\mu}^2$ the variance of the scale factor for cluster μ; r_μ is the estimated overall rate of firing for this cluster. Combining with the likelihood function gives the posterior probability density, which can readily be marginalized (integrated) over all values of the amplitude scale factor A, because it is a Gaussian function of A [9]. Maximizing over μ and t_1 then identifies the most probable spike and its firing time.

Multiple Spikes

In principle, one could extend the method of the preceding subsection to compare the probabilities of all possible combinations of two or more

spikes. Such an exhaustive approach, however, quickly becomes impractical. Instead, note that even if an event contains multiple spikes, the steps in outlined above still identify that template whose subtraction would lead to the largest increase in the probability that the remaining waveform is noise. Thus, instead of the exhaustive approach, one can use an iterative (matching-pursuit or "greedy") approach [9, 11]: Starting with a spike event, find the absolute peak, fit it, subtract the fit, and then repeat the process.

Any such iterative process must determine when to stop fitting spikes. After marginalizing the expression for the posterior probability over A and t_1, one can simply divide by a similar expression for the probability that *no* additional spike was present (namely $KP_{\text{noise}}(\mathbf{V})P(\text{no spike})$). The unknown constant K cancels in this probability ratio, as do the rate factors r_μ for all spikes found up to this point. We can then say that fitting an additional spike is justified if the ratio exceeds unity for some μ_* and terminate the fitting loop when that significance test fails.

Cluster Reliability

The last step in Fig. Fig. 2 is to determine which neurons' activities have been reliably captured. No method will succeed in identifying spikes from every neuron; for example, some will generate spikes whose amplitude is too low relative to the noise. Also, some neurons are gradually dying, or otherwise changing character, during an experiment. Various criteria can be imposed at this point to determine which of the templates' inferred spike trains should be trusted and retained for later analysis [9].

Value of Bayesian Approach

The preceding discussion may have given the impression that the key elements in spike sorting are mathematical. On the contrary, it is the resolving power of the MEA approach itself, combined with the planar geometry of the retina, that permit such thorough spike identification. The Bayesian method described here merely helps to use this resolving power to greatest advantage.

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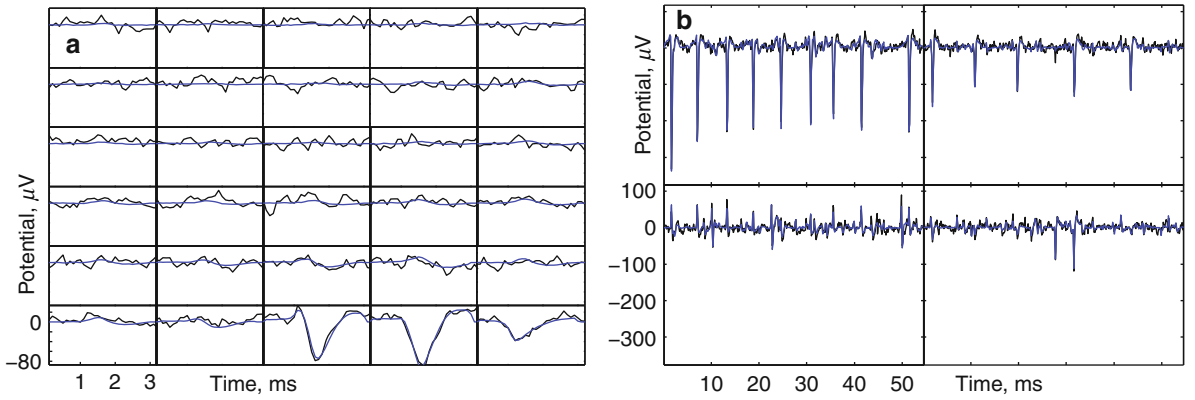
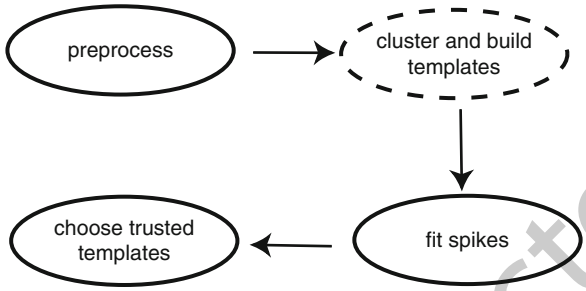
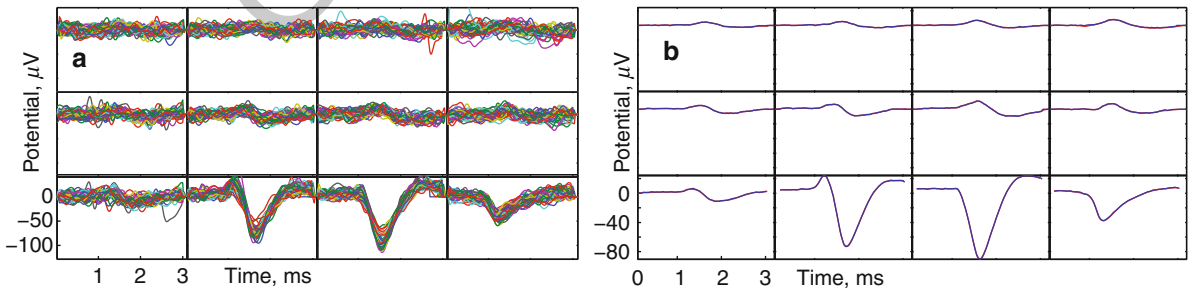


Neural Spikes, Identification from a Multielectrode Array, Fig. 1 (**a**) Example of a single-spike event. Each subpanel shows the time course of electrical potential (in μV, *black curves*), on a particular electrode in the 5 × 6 array. The electrodes are separated by 30 μm (similar to RGC spacing). *Blue curves* show the result of spike sorting, in this case a single template waveform representing an individual neuron. (**b**) Detail of a more complex event and its fit, in which a single neuron fires a burst of nine spikes of varying amplitudes (*upper left channel*), while a different neuron fires five other spikes (*upper right channel*)



Neural Spikes, Identification from a Multielectrode Array, Fig. 2 Schematic of spike sorting method



Neural Spikes, Identification from a Multielectrode Array, Fig. 3 (**a**) Detail of 40 of the aligned exemplars used to compute a template, showing the potential on 12 neighboring electrodes. Some outlier traces reflect events in which this neuron fired together with some other neuron; the unwanted peaks occur at random times relative to the one of interest, and thus do not affect the template. (**b**) *Blue*, detail of template waveform generated from (**a**). *Red*, for comparison, the pointwise mean of the 430 waveforms used to find this template. (The red and blue traces are too close to discriminate visually)