An approximate maximum *a posteriori* approach to separating distinct populations of post-synaptic events

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Introduction

Recordings of synaptic currents are an important source of information about neuronal physiology and behaviour. A single record can include responses to stimuli from multiple synapse types, potentially providing data on interactions among the underlying systems. However, data with multiple overlapping event types is analytically challenging. It is common to address this using pharmacological or other constraints to simplify the recorded activity, but there is a risk of disrupting important interactions, giving misleading results.

Methods for analysing complex synaptic current records are relatively underdeveloped, with the most popular approaches relying on peak detection by such means as threshold crossing and template matching. Somewhat more sophisticated variations have recently been applied in specific cases [1,2], but these remain of limited utility for more complex records. Existing methods are not able reliably to distinguish mixed event classes with overlapping time courses.

Here we describe a new model-based approach to the identification and classification of multiple event classes within a single record, provided the event current time courses can be reasonably approximated by a sum of exponentials.

Signal model

Event currents of a given class are modelled as a weighted sum of non-negative conductance components, $C^{(\cdot)}$. Each component decays with an exponential time course, approximated by a geometric decay constant $\xi^{(\cdot)}$. The contribution weights $\alpha^{(\cdot)}$ are constant, and may be negative. Input events (such as vesicle release) add an equal amount φ to all components (Figure **A**).

Currents from different event classes combine additively, and the signal is corrupted by noise ε, assumed Gaussian with mean 0. If there are n event classes, each having m_i components, the overall signal vector x_t is given by:

$$x_t = \varepsilon_t + \sum_{i=1}^{n}\sum_{j=1}^{m_i} \alpha^{(i,j)} \left(\xi^{(i,j)} C_{t-1}^{(i,j)} + \varphi_t^{(i)}\right)$$

The constants $\alpha^{(\cdot)}$ (up to an arbitrary scaling factor) and $\xi^{(\cdot)}$ constitute a 'template' for each event class. These must be specified *a priori*, typically by fitting a sum of exponentials to selected well-isolated events in the record.

Inference model

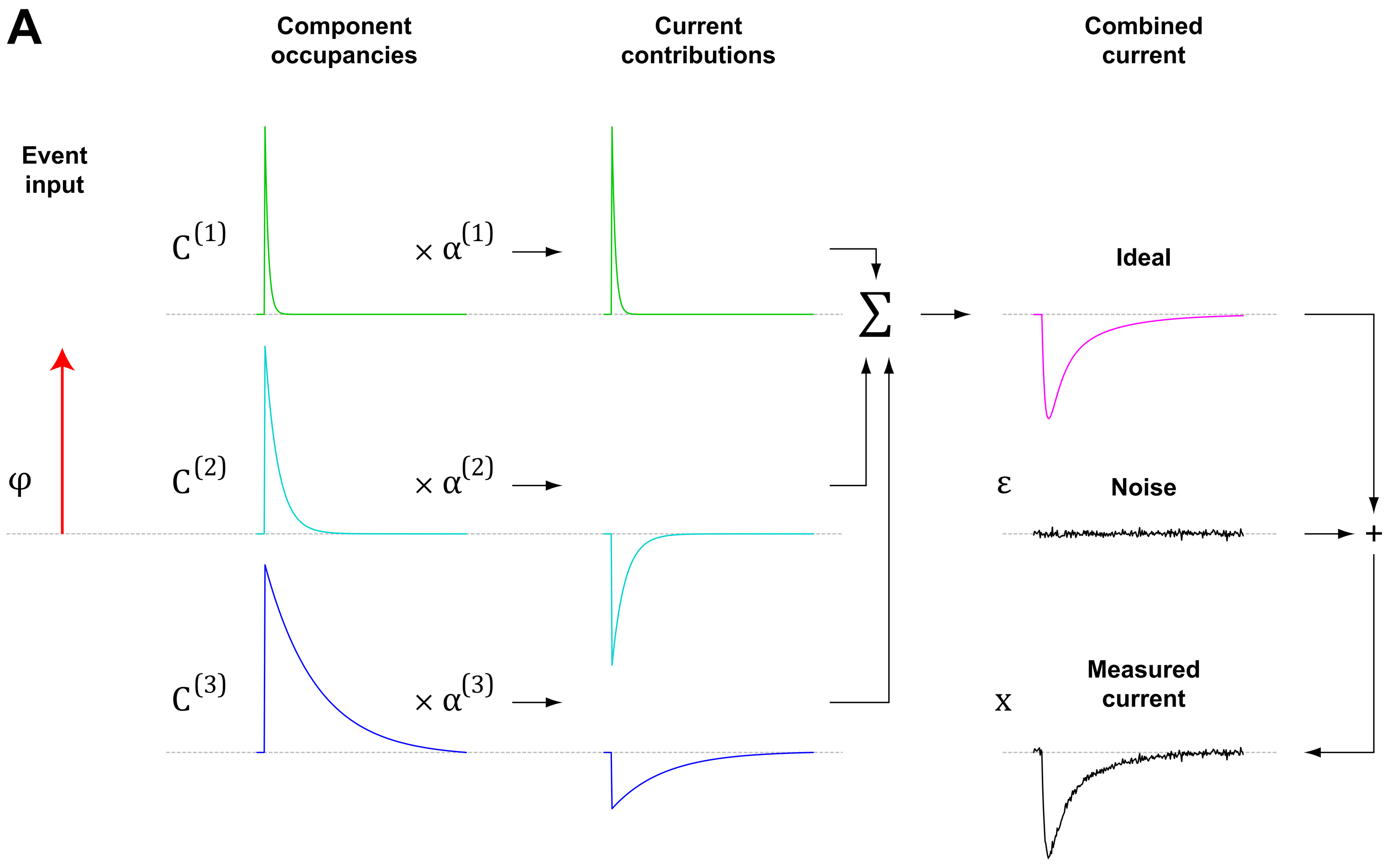
Given an experimental recording x_t, we wish to infer the most probable underlying event train $\hat{\varphi}_t$ or — equivalently but more efficiently — the component decomposition $\hat{C}_t$. A maximum likelihood estimate can be obtained by minimising the residual sum of squares. We do not know the true prior event distribution, but we expect it to be *sparse*. This is imposed by regularisation with the L_1 norm:

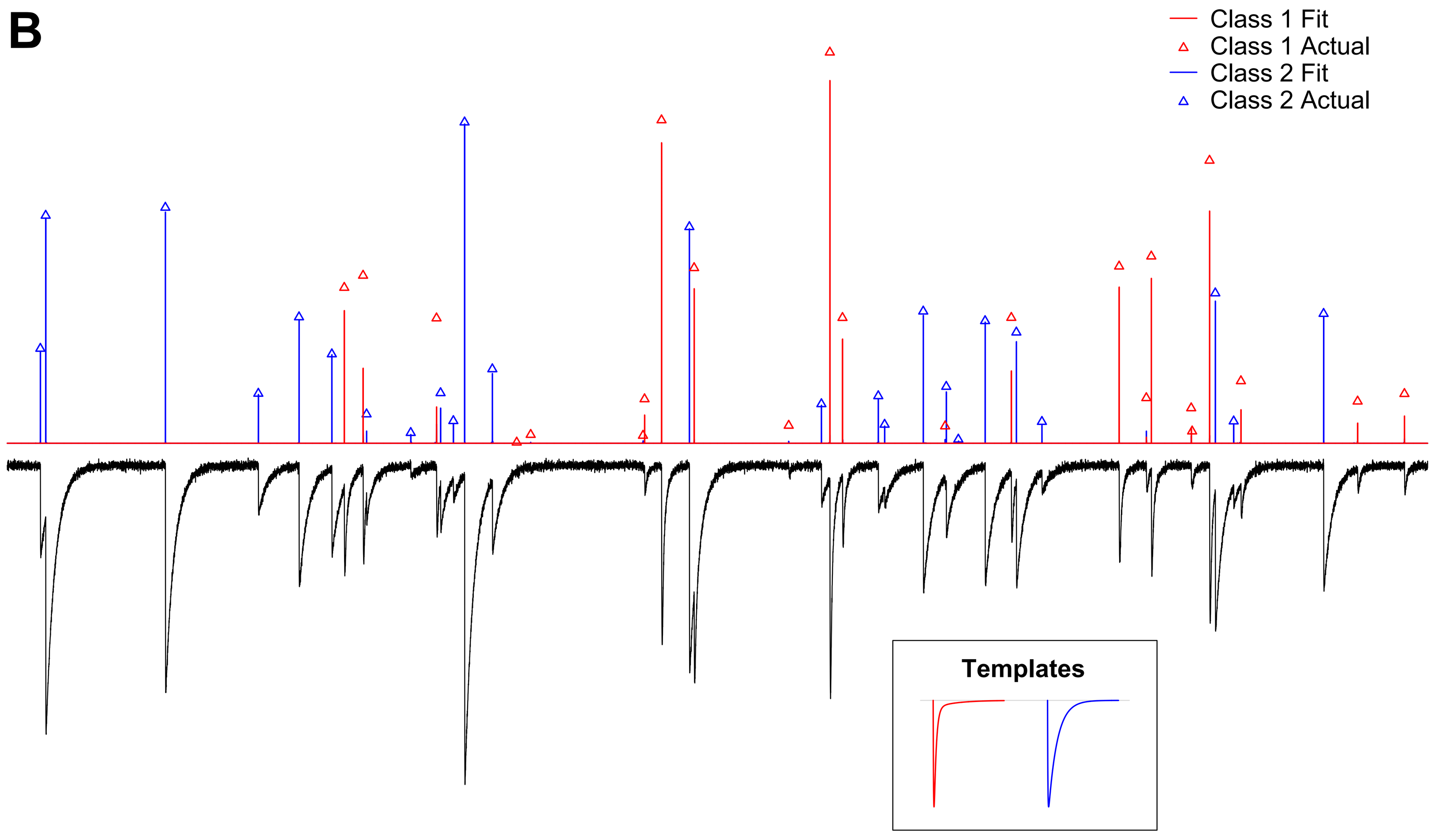
$$\hat{C} = \underset{C \succeq 0}{\operatorname{argmin}} \sum_{t=1}^{T} \left(x_t - \sum_{i=1}^{n}\sum_{j=1}^{m_i} \alpha^{(i,j)} C_t^{(i,j)} \right)^2 + \lambda \sum_{i=1}^{n} \left| C_t^{(i,1)} - \xi^{(i,1)} C_t^{(i,1)} \right|$$

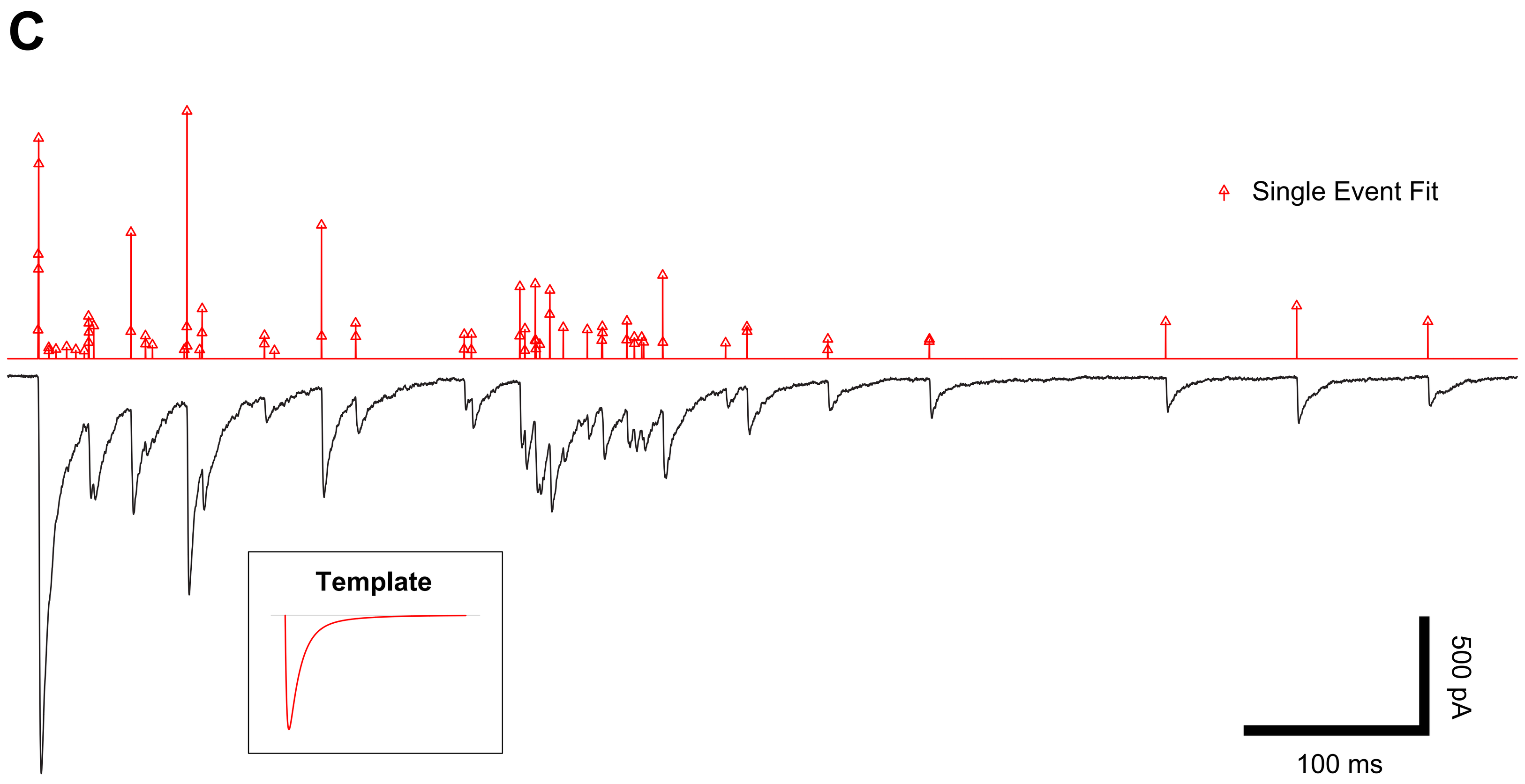
subject to:

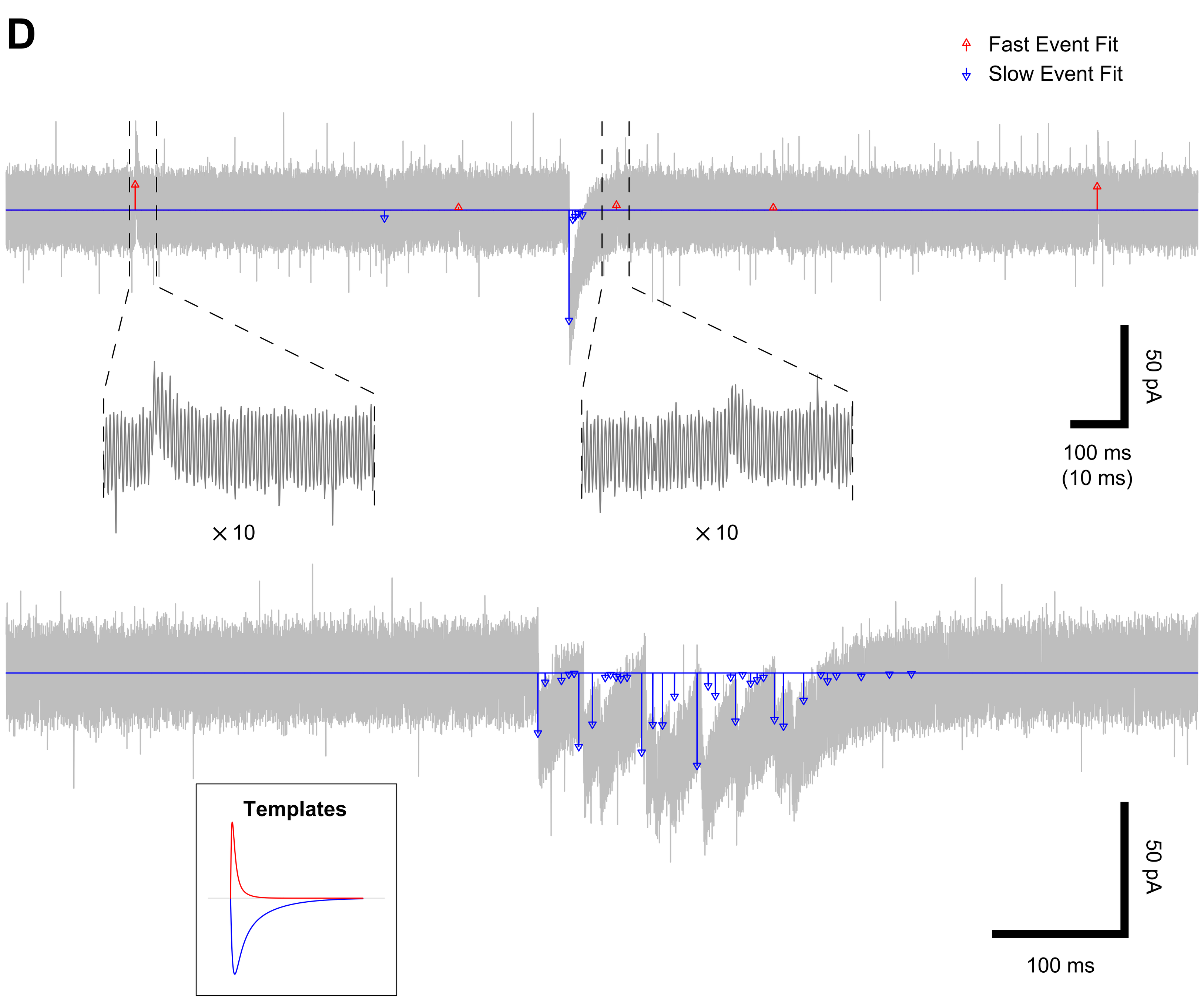
$$C_t^{(i,j)} - \xi^{(i,j)} C_{t-1}^{(i,j)} = C_t^{(i,k)} - \xi^{(i,k)} C_{t-1}^{(i,k)}$$
$$\forall : i \in \{1,\dots,n\},\ j,k \in \{1,\dots,m_i\},\ t \in \{1,\dots,T\}$$

(The additional constraints enforce the equality of φ for all components of a class.) This minimisation appears unwieldy, but it can be formulated as a *second order cone program*, a class of convex optimisation problem for which standard solver tools exist [3].









Simulation results

The forward model can be simulated to provide test data for which the true underlying event trains are known, incorporating a variety of noise levels, event classes and contaminating factors such as baseline drift. Fitting to such data suggests that the original event trains are recovered reliably in many realistic scenarios. An example using two event classes is shown in Figure **B**.

Event times are typically identified with high accuracy, and type classification is also usually reliable except where events are virtually simultaneous. Event amplitudes (estimating the stimulus strength driving the current peaks) tend to be underestimated, to a degree governed by the regularisation parameter λ. A result of the trade-off between overfitting and our sparsity prior, this may be compensated in post-processing.

Experimental results

We applied the fitting procedure to whole cell patch clamp recordings obtained from acutely vibrodissociated rat cerebellar Purkinje neurons [4]. In this preparation most of the dendritic tree is absent and the cell receives inputs only from a few isolated synaptic boutons, primarily from inhibitory interneurons.

In Figure **C**, a single event class was fitted, corresponding to these inhibitory inputs. Interneuron boutons are believed to exhibit multivesicular releases [5,6]. Our fit results are consistent with such behaviour. Notably, large events show a compound rising phase with several events in quick succession, suggesting multiple vesicle releases that are closely but not perfectly synchronised.

In Figure **D**, the cell was held at a voltage between the reversal potentials for cation and anion-mediated currents. The resulting events are small, but can be clearly seen to be going in opposite directions, implying that some excitatory synapses remained active on this cell. The fitting procedure was able to identify and classify events despite the high relative noise level. The true event train is not known, but the events found are persuasive (see enlarged examples). The inhibitory events again show clustering suggestive of multi-vesicular release (lower trace).

Discussion

We have successfully demonstrated that multiple event classes can be identified and separated from at least a subset of mixed synaptic current recordings, via a model-based fitting procedure. Though still a work in progress, this capacity will enable more sophisticated analyses of existing experimental data. Further, by making it possible to analyse and interpret more complex results, it promises to encourage the performance of less constrained, more realistic experiments, allowing the acquisition of better information that will advance our understanding of neuronal function.

References

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