Classification of Postsynaptic Current Events in Purkinje Cells

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Introduction

- Purkinje cells are in the cerebellum.
- They receive excitatory and inhibitory inputs.
  - Postsynaptic current is a **mixture of events**.
    - Fast events.
    - Slow events.
  - Drugs can selectively block receptors.
    - DNQX blocks AMPA receptors (fast events).
    - Bicuculine blocks $GABA_A$ receptors (slow events).
  - But drugs cause artifacts.
    - Blocking one receptor type interferes with normal interactions.
    - Example: where presynaptic receptors mediate retrograde feedback.
- The challenge is to **unmix and classify events** using computational methods.
  - Fast event trains.
  - Slow event trains.
- But first, some background about Purkinje cells and their connectivity.

Inputs to the Purkinje cell.

Excitatory

1) Parallel fibre
2) **Climbing fibre**

Inhibitory

1) Stellate cell
2) **Basket cell**

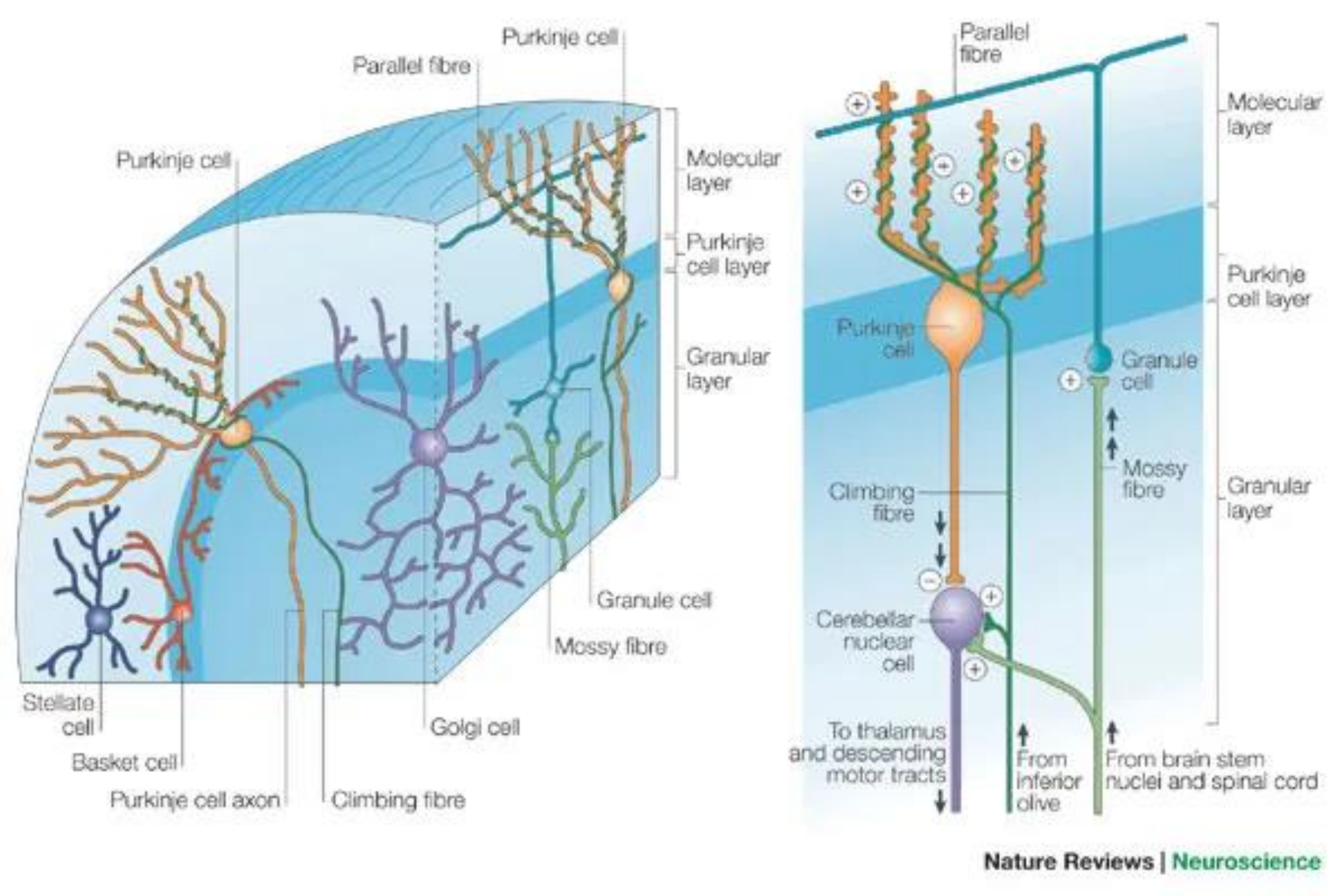
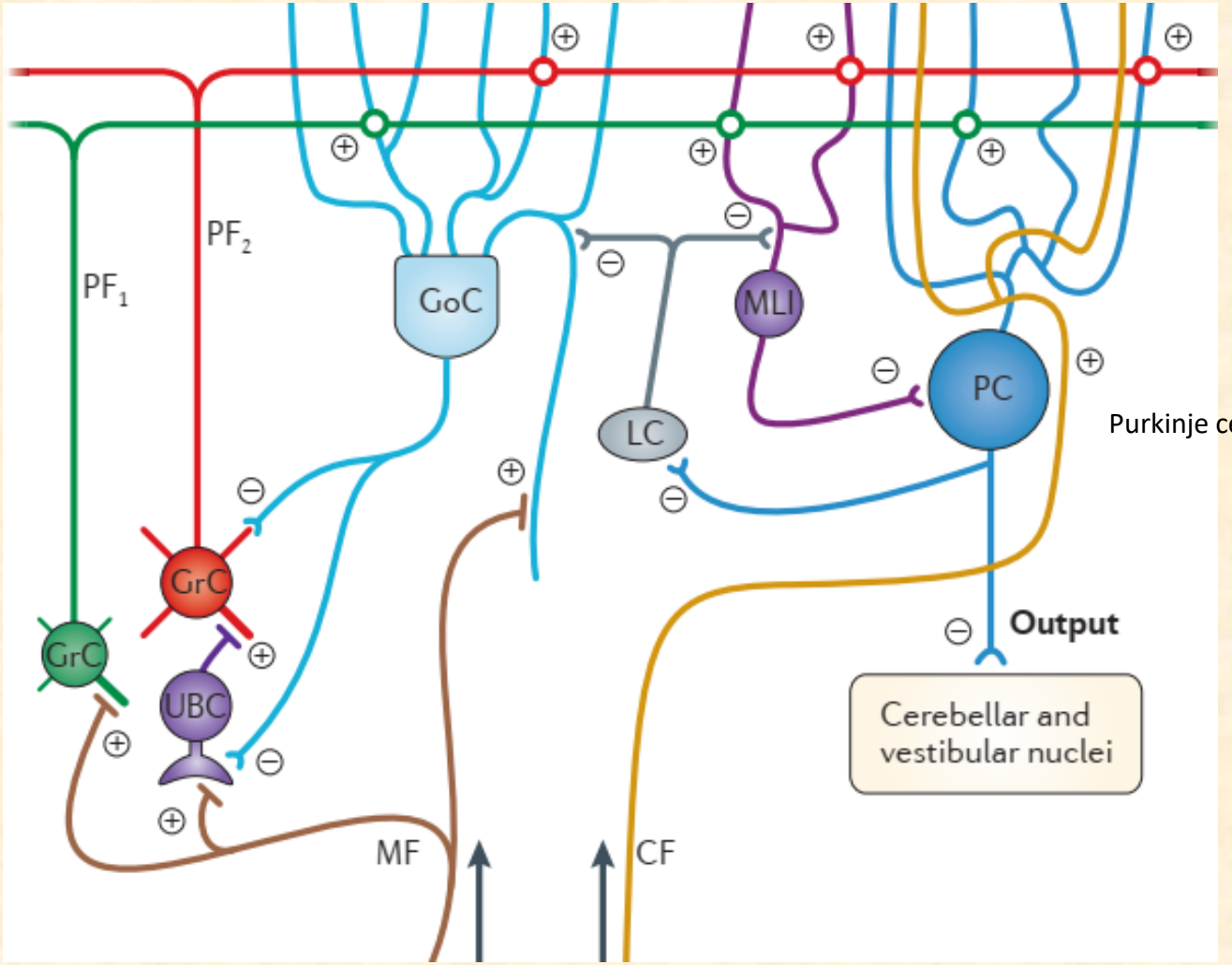


Image: (Apps *et al.* 2005).

Purkinje cell synapses

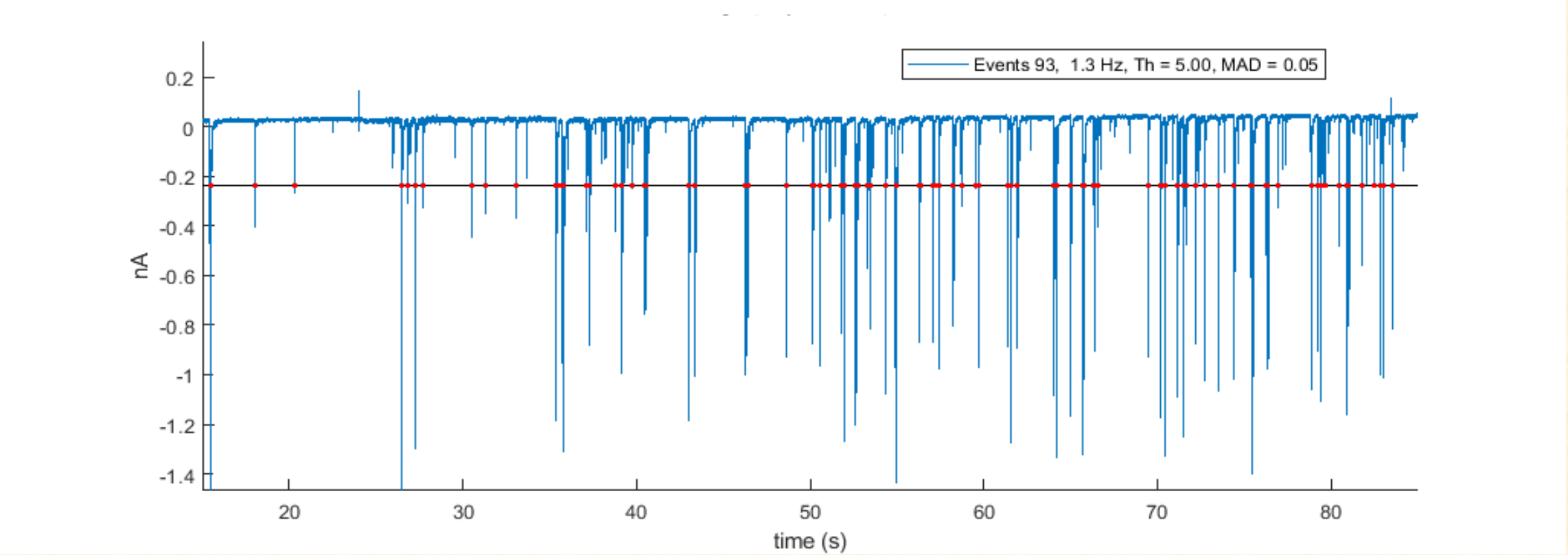
1) Parallel fiber (PF) **(+)**
2) Molecular layer interneuron (MLI)
   a. **basket cells** and stellate cells **(-)**
   b. **presynaptic NMDARs** in basket cell terminals?
3) Lugaro cell (LC)
4) Granule cell (GrC)
5) Unipolar brush cell (UBC)
6) Mossy fibre (MF)
7) Climbing fibre (CF) **(+)**



Purkinje cell (PC)

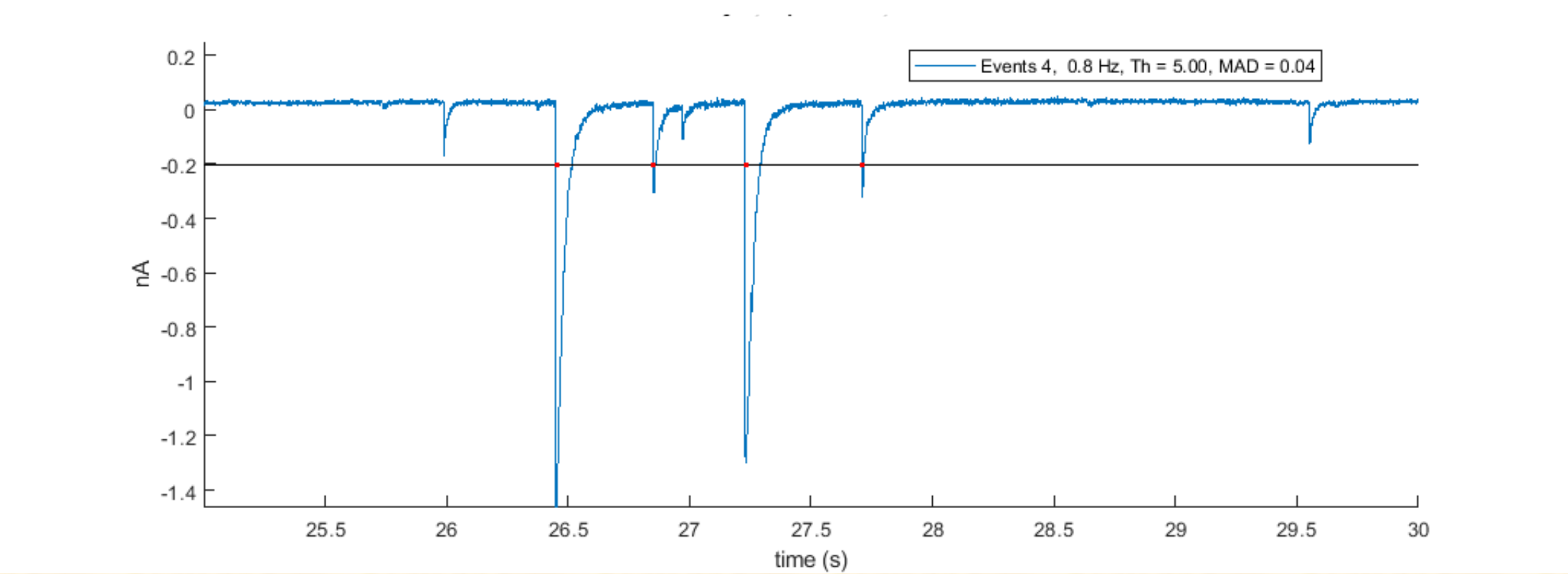
Image: (Gao 2012).

Event Train



File 09921004.abf: DNQX and NMDA at 37.45 seconds.

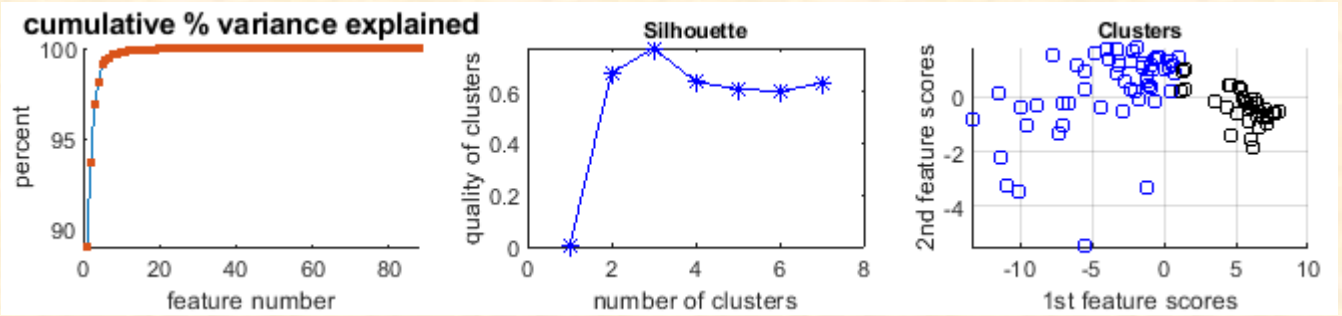
Event Train Before DNQX



File 09921004.abf: zoom in to see shape of PSCs. Here events to do not overlap**, no fast events?**

Post Synaptic Waveform Sorting

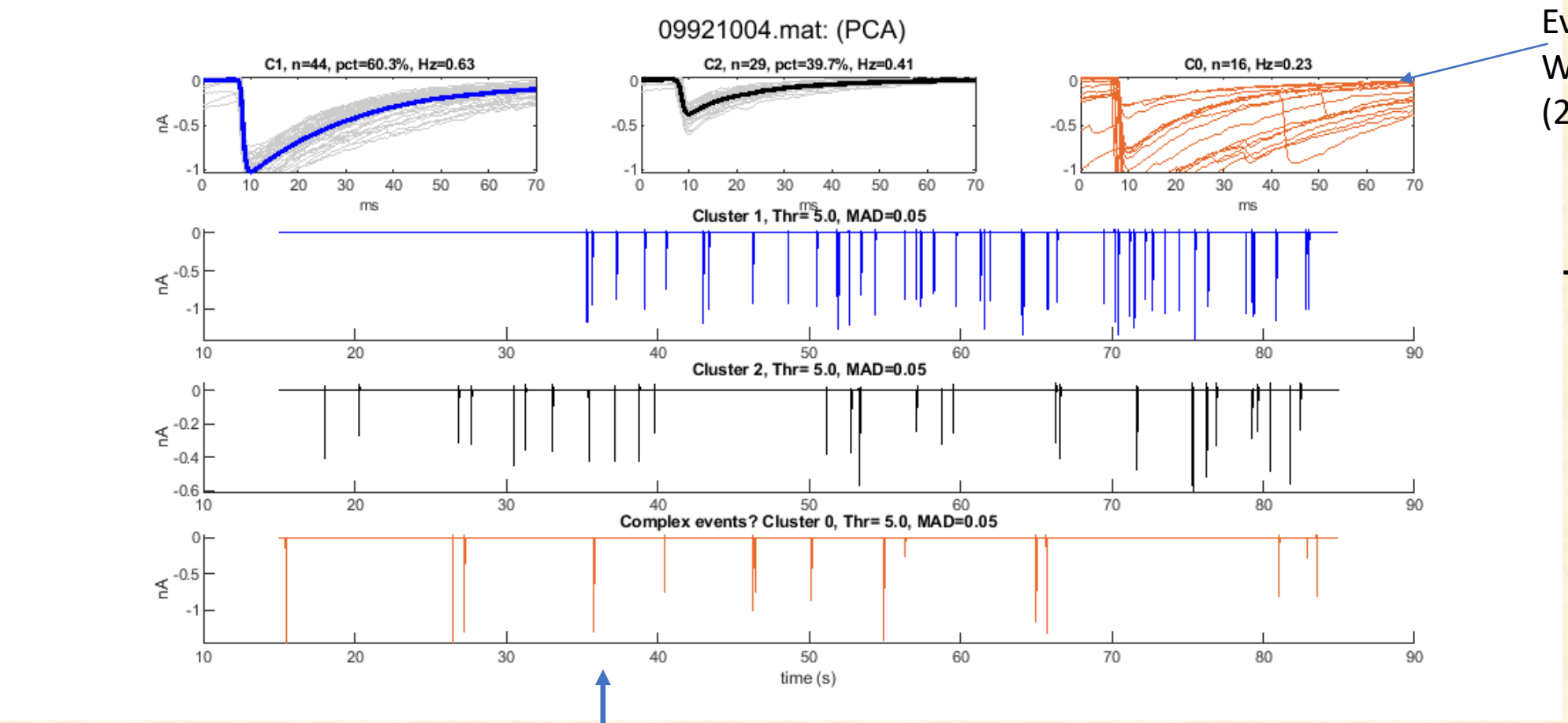
- Event detection
  - Filter data if necessary.
  - Amplitude threshold to get candidate waveforms.
- Feature extraction and visualisation
  - Principal Components Analysis (PCA).
  - K-means clustering using the squared Euclidean distance metric.



K=2

  - Compute mean waveform for each cluster and the plot event trains.

Mean Waveforms and Event Trains



Evicted Waveforms (2.5 std)

T=5.0

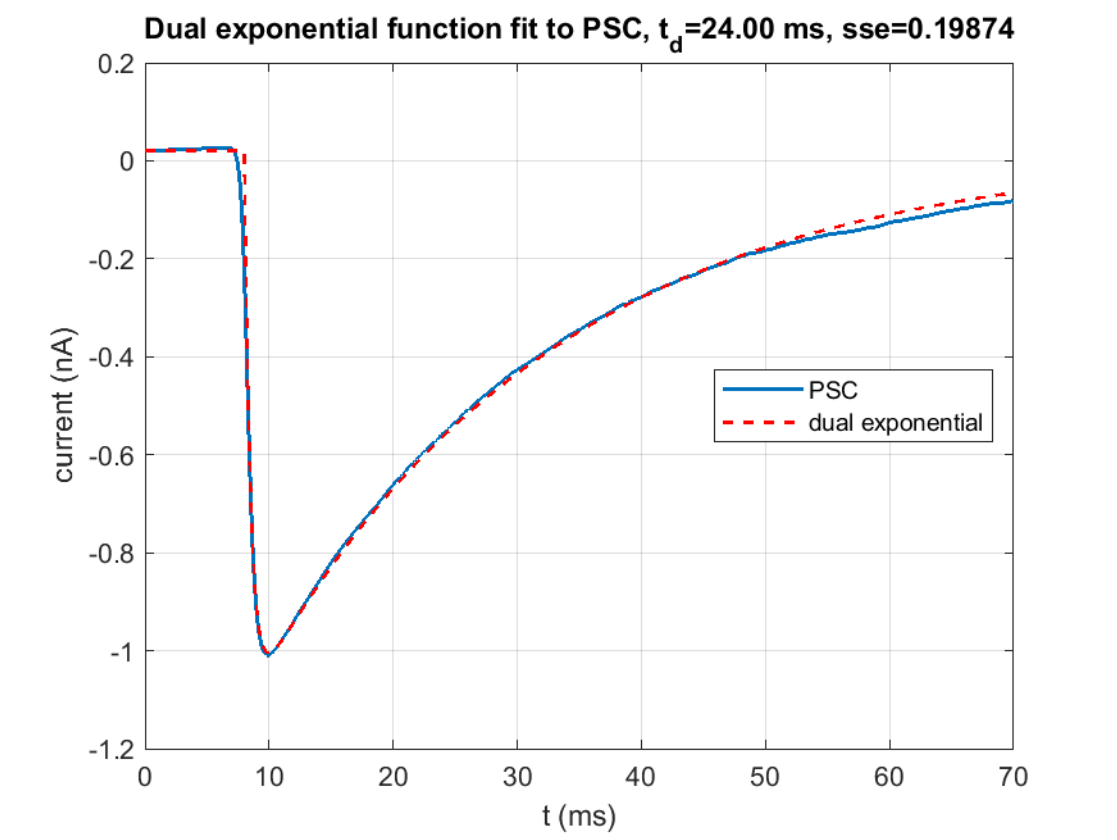
DNQX and NMDA at 37.45 seconds.

Build Template Library: fit dual exponential function

$$I(t) = I_{max}\frac{\tau_d\tau_r}{\tau_d - \tau_r}\left(exp\left(-\frac{t-t_s}{\tau_d}\right) - exp\left(-\frac{t-t_s}{\tau_r}\right)\right)$$

Current **I(t)** depends on the rise and decay time constants.

After DNQX: t_r = 5 ms, t_d = 24 ms



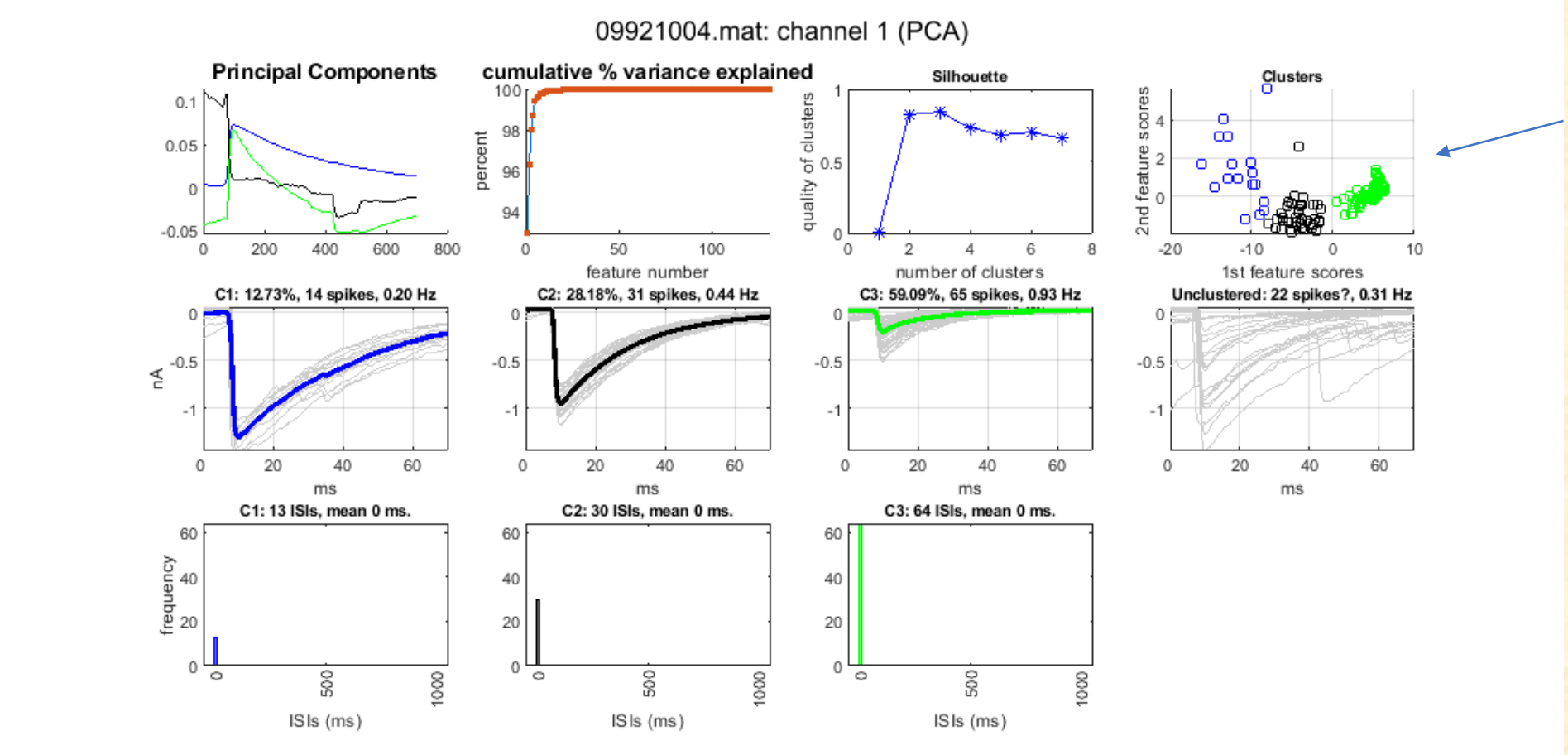
Next Steps

- Slide templates along old **or** new data to detect and classify events.
- Use synthetic data for testing.
- Do computational analysis of data sets in context of pharmacological data.

- Additional methods?
  - Bayesian methods
    - Exploit prior knowledge about the data.
  - Machine learning
    - Neural networks for pattern recognition.
      - Learn from labelled examples
    - ?

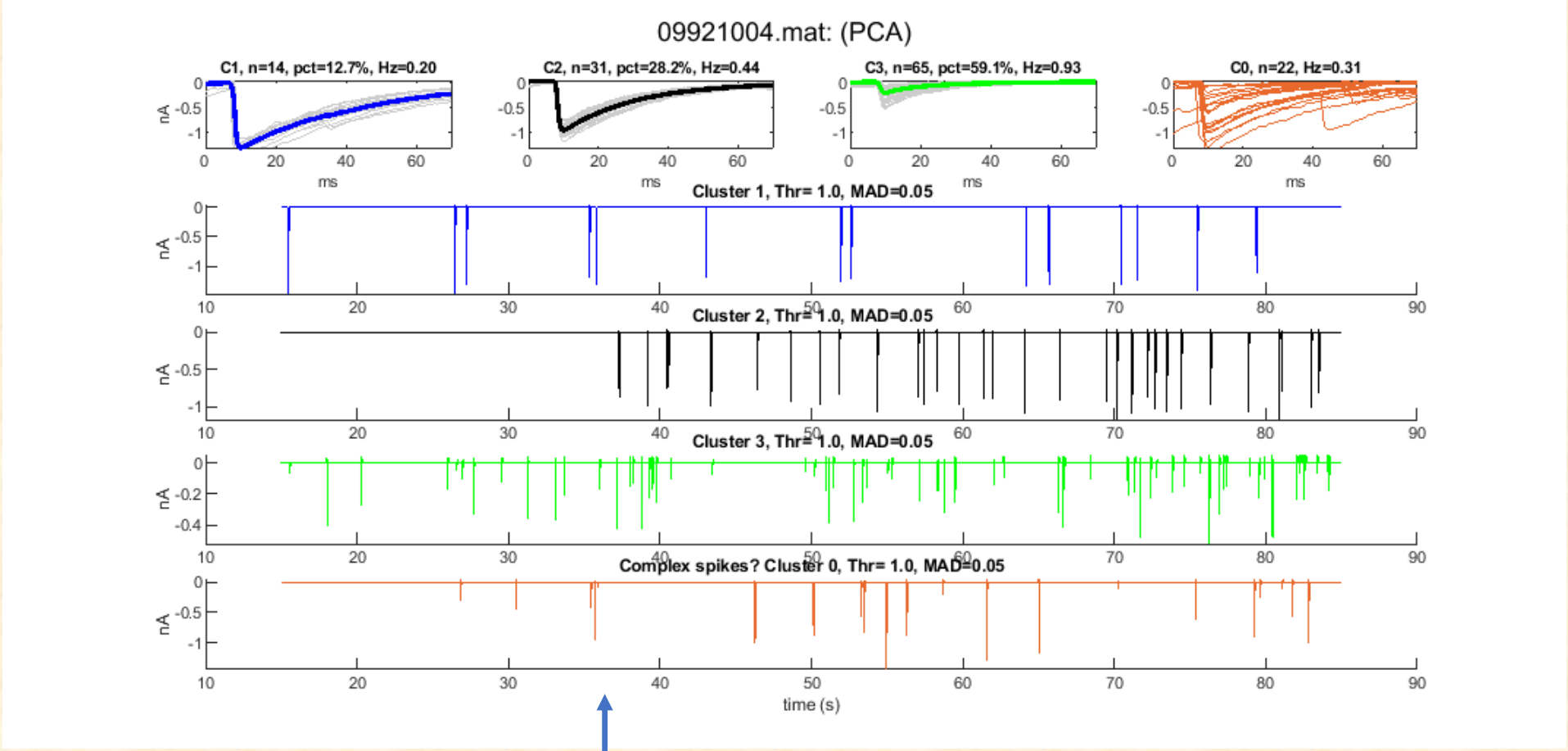

END

Sorting: using K=3 and T=1



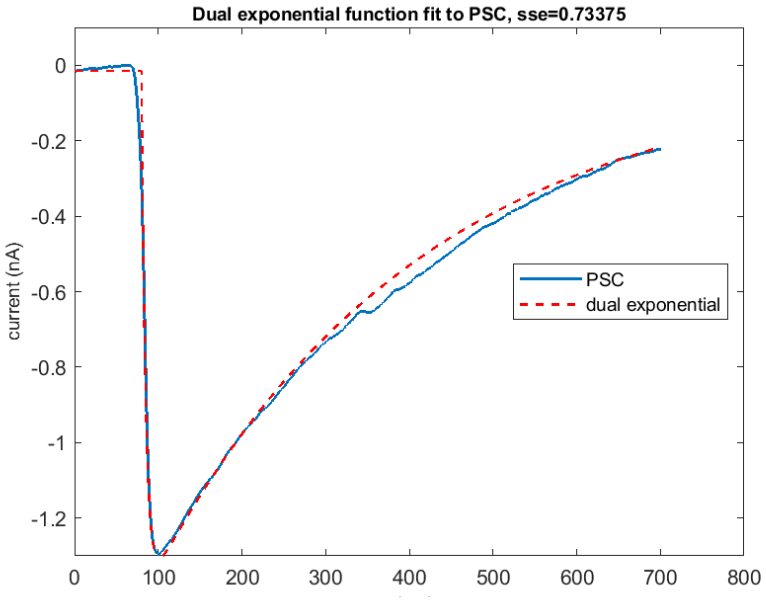
3 distinct clusters

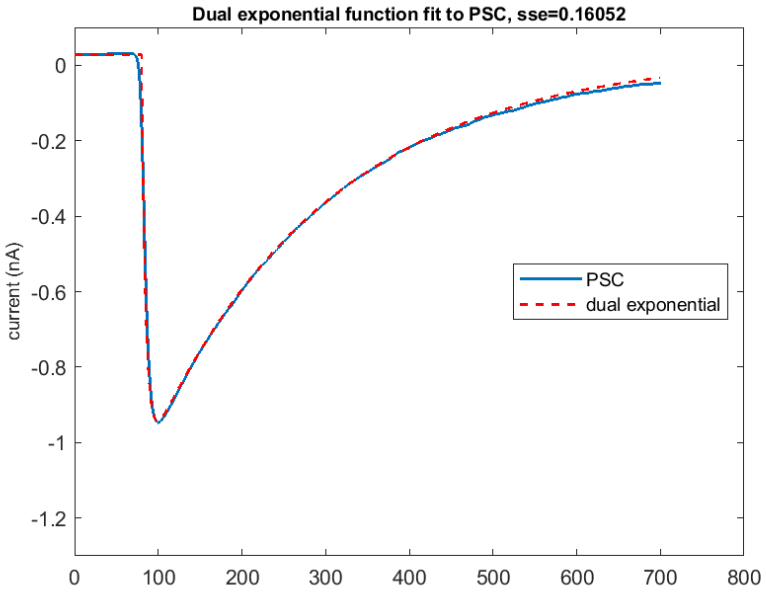
Event Trains: used K=3 and T=1

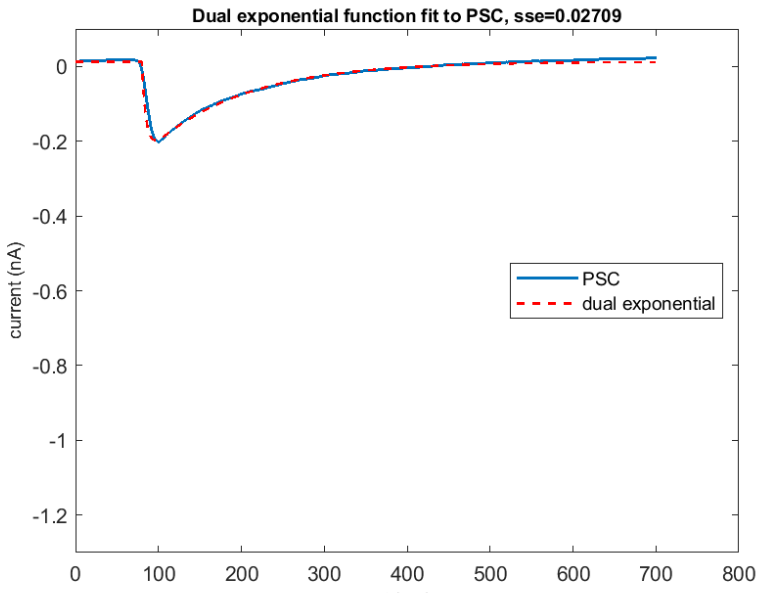


DNQX and NMDA at 37.45 seconds.

Slow templates: used K=3 and T=1







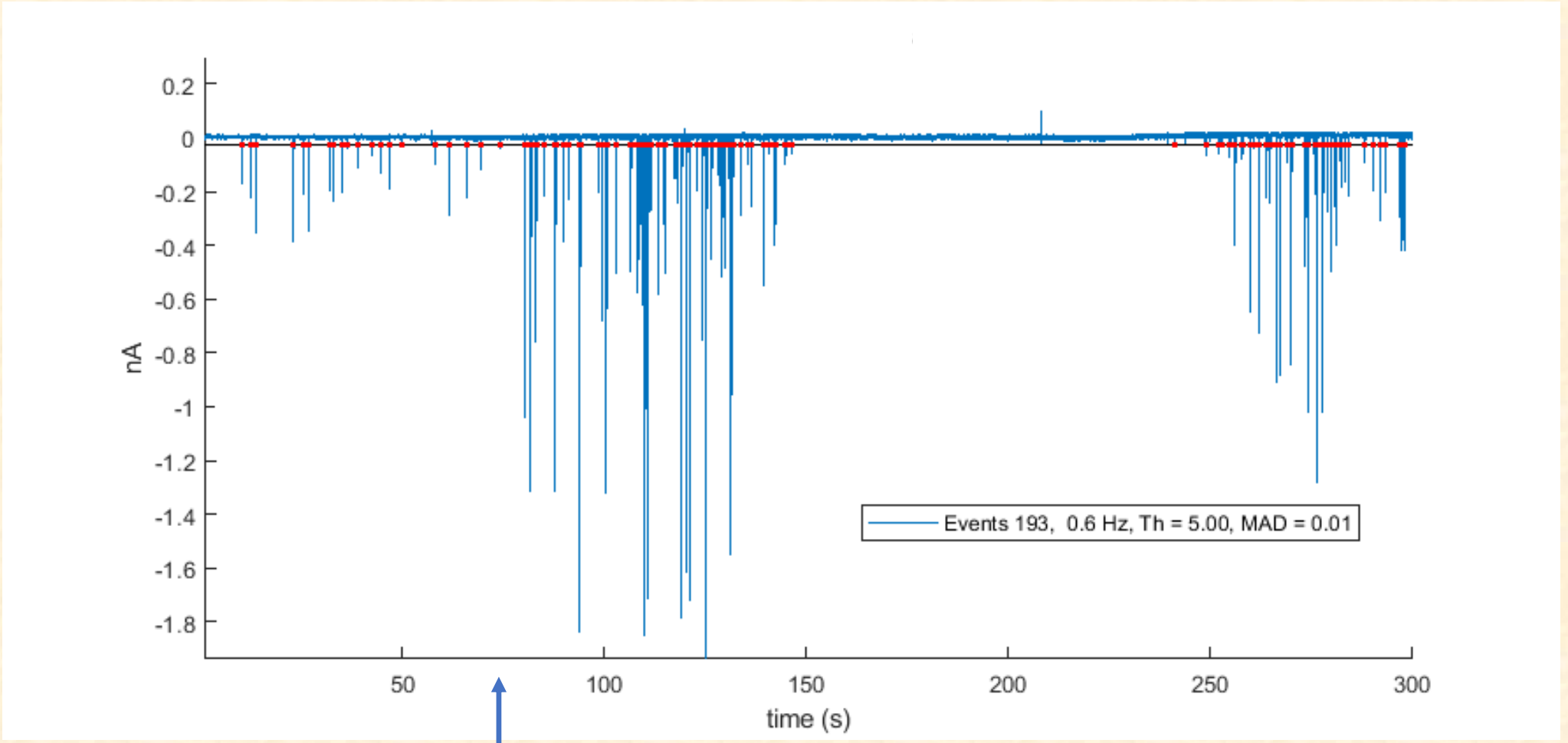
X axis in time steps, 10 steps per ms

Cluster 1: t_d = 32 ms

Cluster 2: t_d = 22 ms

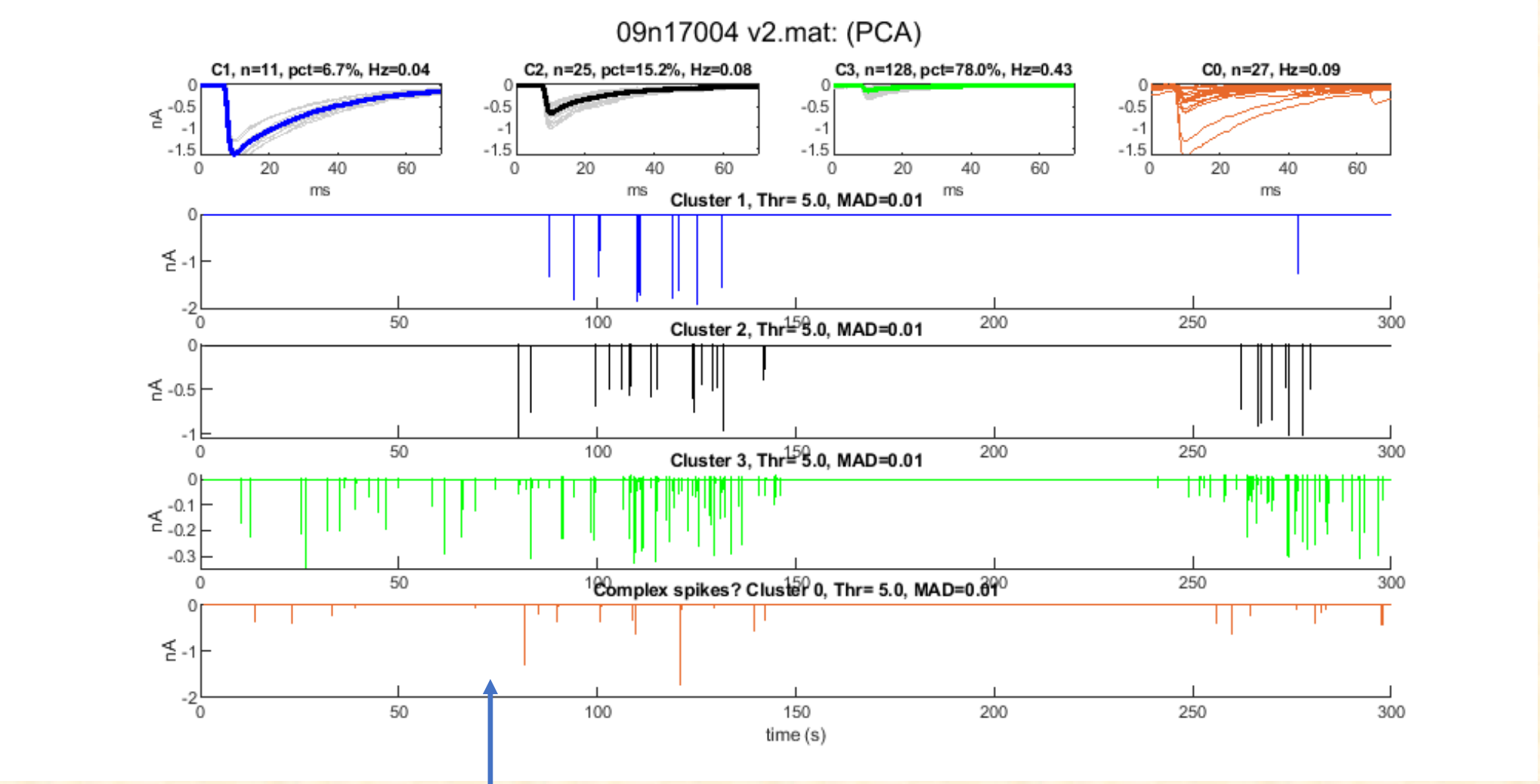
Cluster 3: t_d = 11 ms

300 seconds, T=5



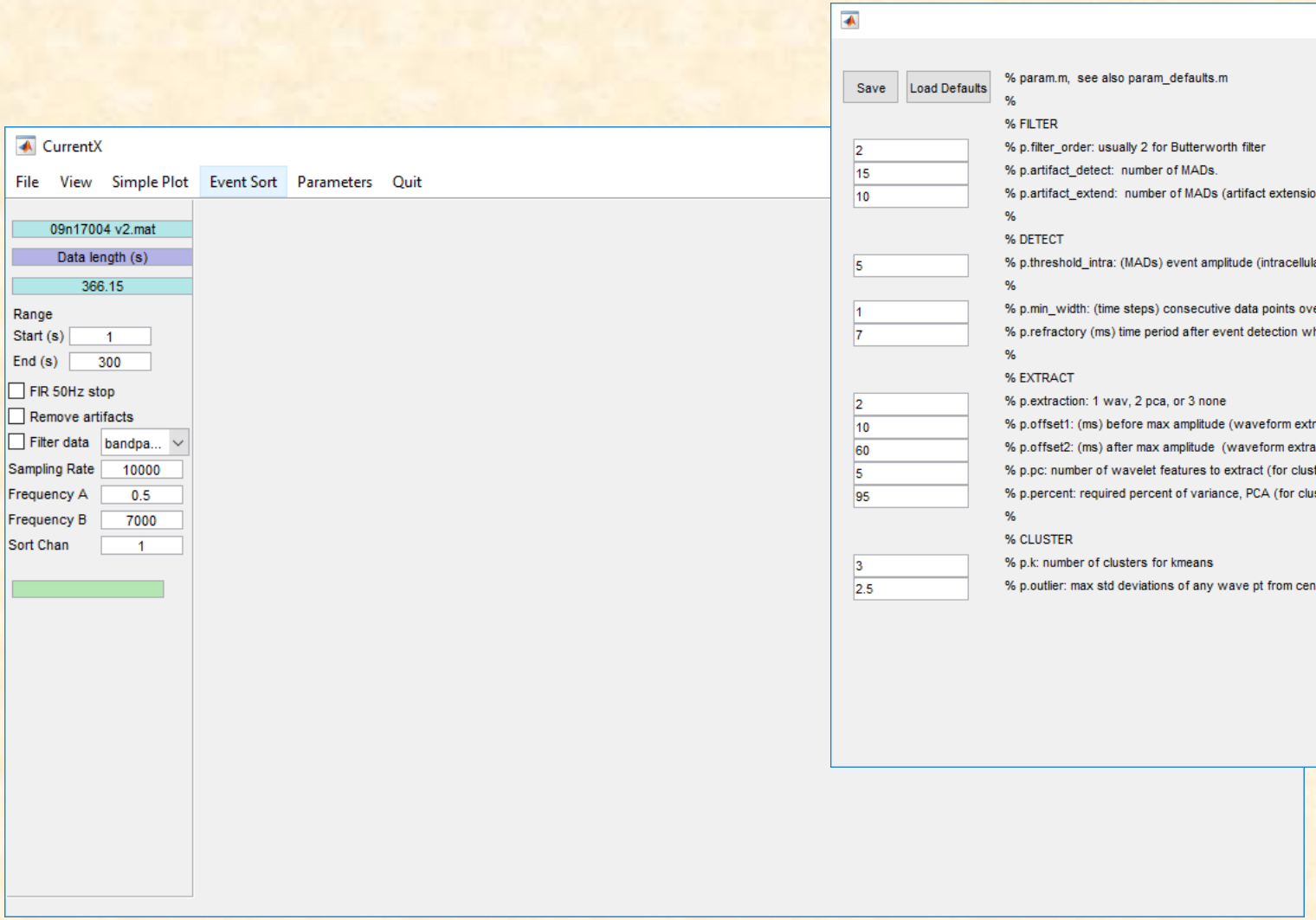
File: 09n17004 v2: DNQX and NMDA at 71.85 seconds.

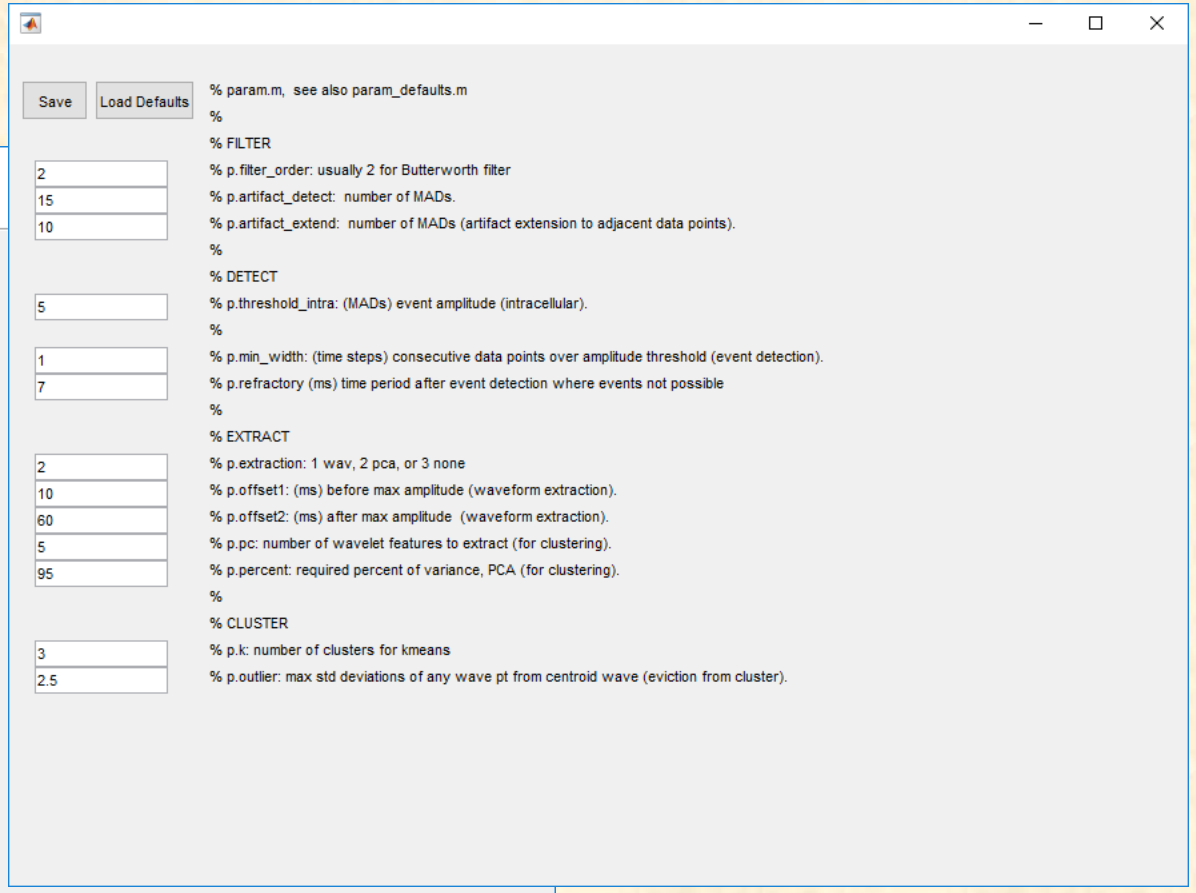
300 seconds, K=3, T=5



DNQX and NMDA at 71.85 seconds.

CurrentX GUI and Parameters





References

- Duguid, Ian C and Smart, Trevor G, **Retrograde activation of presynaptic NMDA receptors enhances GABA release at cerebellar interneuron-Purkinje cell synapses**, Nature neuroscience, 2004
- Apps, Richard and Garwicz, Martin, **Anatomical and physiological foundations of cerebellar information processing,** Nature reviews. Neuroscience, 2005.
- Gao, Zhenyu and van Beugen, Boeke J and De Zeeuw, Chris I, **Distributed synergistic plasticity and cerebellar learning**, Nature reviews. Neuroscience, 2012.