Four Types of Brain Cells Identified Based on Electrical Spiking Activity

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The material in this tutorial is based in part on the work presented in [1] and my own *research. For more information, please write to Rashvand_Ashkan@email.kntu.ac.ir.*

Brain neural cell classes identification ,is key to understanding brain function . this topic is typically overlooked in electrophysiological studies .
Neurons have diverse molecular, morphological, connectional and functional properties.
Recently researchers in Germany and the United States managed to classify four distinct types of neurons based on their electrical spiking behavior. This classifications could help researchers better understand how these types of neurons function, and lead to more precise methods for treating psychiatric disorders.
Deep brain stimulation for Parkinson's disease and epilepsy is the benfits of this research.

Introduction

Cell-type-specific neuronal properties shape characteristic circuit oscillations associated with various computational and cognitive processes.

Thus, knowledge about cell types and their role in cortical
circuits is key to understanding brain function.

From litreture review , so far waveform width has been shown to be informative about cell-type diversity in the primate brain, allowing to dissociate two broad classes of putative cell types (excitatory versus inhibitory).

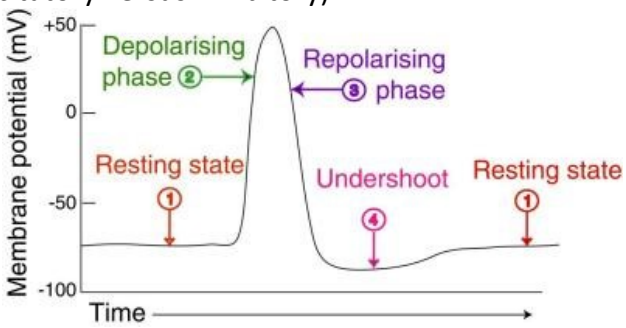


Figure 1 spike waveforms of extracellular

During this research, in order to better understand cell-type-specific mechanisms and functions, more cell types
need to be identified. Furthermore, cell-type classification needs
to be compared across different cortical regions.

To address this, they characterized putative cortical cell types
based on spike waveforms in a large dataset of extracellular recordings from three different cortical regions (FEF, dorsolateral prefrontal cortex [dlPFC], and lateral intraparietal area [LIP]) in
two macaque monkeys

In contrast to the typically reported dichotomy between broad-spiking and narrow-spiking units, we were able to distinguish four cell classes based on
waveform shape. These four distinct cell

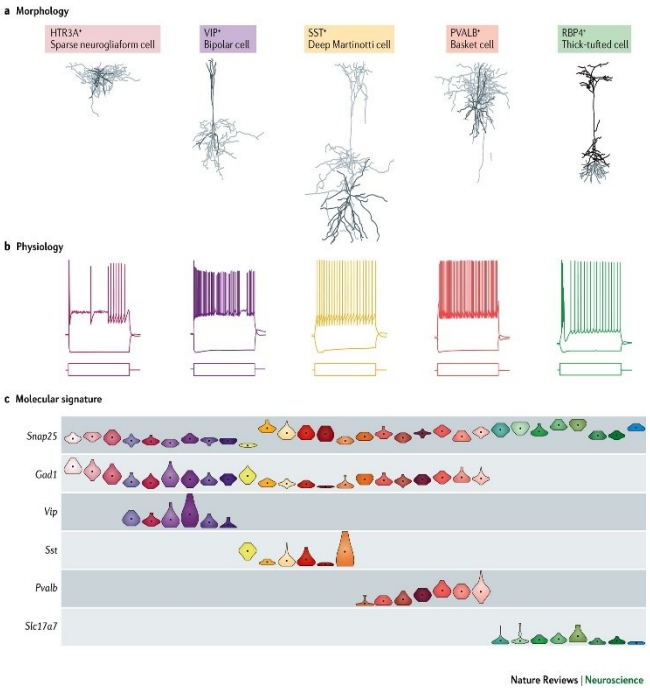
classes were confirmed by cell-class-specific firing patterns, response dynamics, and information coding. Although the four cell classes
were consistently found across all cortical regions, their functional profiles differed between areas.

Purposes of cell-type classification

Few neuroscientists view neuronal classification as an end in itself. Rather, they hope that development of a cellular taxonomy will facilitate their understanding of how the brain works or, in diseases, fails to work prop- erly. Designing a useful classification scheme therefore requires making explicit the needs it is meant to fulfil.

Clasical defining neuronal types

In principle, it seems obvious that neurons should be viewed as members of a type if they serve a function that differs from the functions of other types of neurons. In practice, however, the functions of individual neurons can seldom be determined. Moreover, some functions may emerge only at the level of circuits. We therefore sug- gest that a more useful definition of type is a population of neurons with properties that are homogeneous within the population but differ from those of other neurons. What are the relevant properties? The three main categories are morphological, physiological and molecular:



Electrophysiological method detail

Electrophysiological recordings:
Extracellular signals were recorded in 70 recording sessions in two rhesus monkeys using Tungsten microelectrodes simultaneously inserted in FEF, dorso-lateral PFC, and LIP.

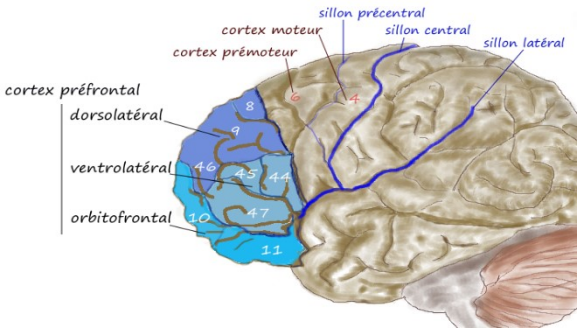


Figure 2FEF, dorso-lateral PFC, and LIP

Waveform preprocessing:
To obtain spike waveforms, they extracted segments of the filtered voltage traces in a window of 3 ms around each noise thresholdcrossing (4 SD; 1 ms before crossing) aligned on the main trough of the waveform. The noise level (SD) was robustly estimated as 0.6745 times the median of the absolute of the filtered data.

Waveform clustering:
As features for cell class classification, they computed two measures of waveform shape: trough-to-peak duration and time for repolarization. Trough-to-peak duration is the distance between the global minimum of the curve and the following local maximum. Time for repolarization is the distance between the late positive peak and the inflection point of the falling branch of the curve.

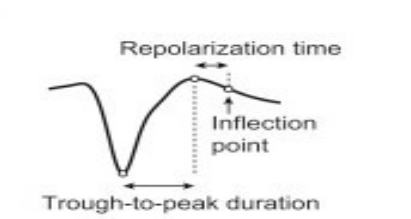


Figure 3trough-to-peak duration and time for repolarization

To identify clusters in the data in an unsupervised way, they used the expectation-maximization (EM) algorithm for Gaussian mixture model (GMM) clustering. they modeled the data as a weighted sum of multivariate Gaussians:

$$P(x) = \sum_k \pi_k N(x|\mu_k, \Sigma_k)$$

with k components parametrized by mean m, covariance μ_k and mixing coefficient p.
The EM algorithm fits this model by iteration of a two-step process: it first estimates posterior probabilities of the data given the current set of parameters (E step), and then updates the parameters to maximize the log-likelihood function of the model given the current estimates (M step). The steps are repeated untilconvergence.
They initialized the process with random parameters for 50 repetitions and chose the fit with the largest log-likelihood among the replicates.
To select the number of Gaussian components in the model they used the Bayesian information criterion (BIC):

$$BIC = -2lnP(x|\theta) + k \ln(n)$$

where $P(x|\theta)$is the maximized likelihood for the estimated model, K is the number of parameters, and n is the sample size.
By including a penalty term that grows with the number of parameters, the BIC cost function effectively favors simpler models and reduces overfitting.
The optimal number of clusters was chosen as the value that minimized the BIC computed between 2 and 10 components.

Analysis of firing statistics:

To characterize spontaneous activity, we analyzed spiking activity during the baseline fixation period. We averaged across baseline periods of all trials. We computed four firing statistics: mean firing rate across trials (FR), Fano factor (variance over mean of spike counts across trials, FF), coefficient of variation of the inter-spike interval distribution (CVISI) and burst index (BI). Both Fano factor and CVISI are mean-standardized measures of dispersion that reflect firing regularity, with an expected value of 1 for Poisson firing and values below 1 indicating more regular firing.
Classification procedure:

To reduce the multiclass problem to binary classification, we independently trained and tested six binary SVMs for each pair of cell classes. The six sets of predicted labels were combined by majority vote (‘one-versus-one’ classification).
Cross-area classification:

To assess area specificity of cell class decoding, we trained classifiers on data from one cortical area and used them to predict data from other areas.

Principal component decomposition of PSTH:

In neurophysiology, peristimulus time histogram and poststimulus time histogram, both abbreviated PSTH or PST histogram,

are histograms of the times at which neurons fire.
Peristimulus time histograms (PSTH) of single-unit spike counts were computed using 50 ms bins, within a 1.5 s trial window comprising the 0.5 s baseline fixation period and the 1 s cue period.

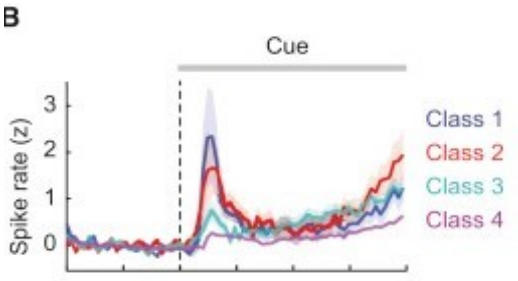


Figure 4 PSTH

Overview and Benefits of this method rather than others:

The advance offers brain researchers the chance to better understand how different kinds of neurons are contributing to behavior, perception, and memory, and how they are malfunctioning in cases of psychiatric or neurological diseases. Much like mechanics can better understand and troubleshoot a machine by watching how each part works as it runs, neuroscientists, too, are better able to understand the brain when they can tease apart the roles different cells play while it thinks. At best, neuroscientists have so far only been able to determine from electrophysiology whether a neuron was excitatory or inhibitory. That's because they only analyzed the difference in the width of the spike. The typical amount of data in an electrophysiology study spikes from a few hundred neurons only supported that single degree of distinction. But the new study could go farther because it derives from a dataset of recordings from nearly 2,500 neurons. Researcher gathered the data years ago at MIT from three regions in the cortex of animals who were performing experimental tasks that integrated perception and decision-making. thus, the team decided to put the dataset through a ringer of sophisticated statistical and computational tools to analyze the waveforms of the spikes. Their analysis showed that the waveforms could actually be sorted along two dimensions: how quickly the waveform ranges between its lowest and highest voltage ("trough to peak duration"), and how quickly the voltage changes again afterward, returning from the peak to the normal level ("repolarization time"). Plotting those two factors against each other neatly sorted the cells into four distinct clusters.

Cell-Class Separation Based on Spike Waveform

To identify different cell classes in an unsupervised way, they performed a two-dimensional cluster analysis of the waveform parameters (Gaussian mixture model). they used the Bayesian information criterion (BIC) to select the number of Gaussian components in the model. The BIC showed a global minimum for four components indicating four distinct waveform classes.

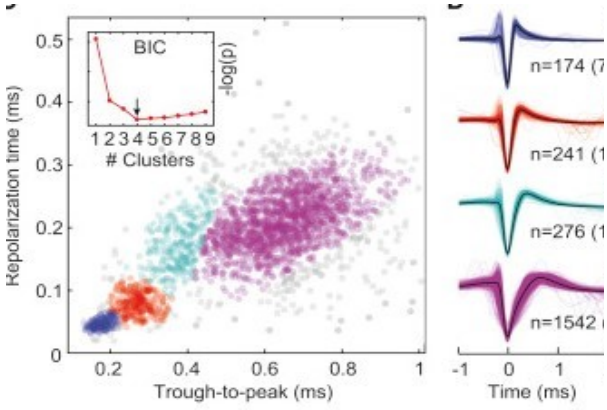


Figure 5 four distinct waveform classes

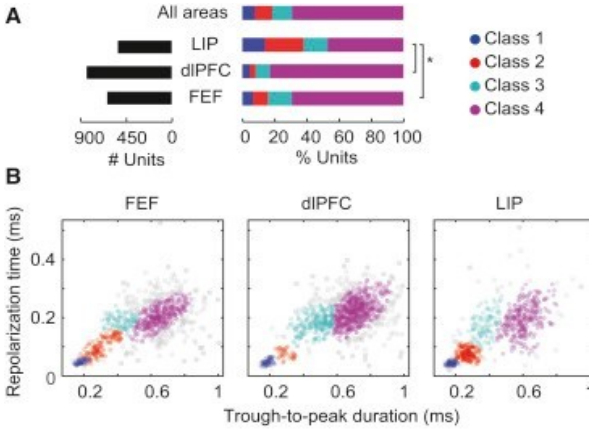


Figure 8four classes across cortical regions

They quantified cluster separation by calculating the probability of correctly classifying each cell class based on the Gaussian mixture model underlying the clustering .

The average classification accuracy across all four classes was 94%, indicating well-separated clusters.

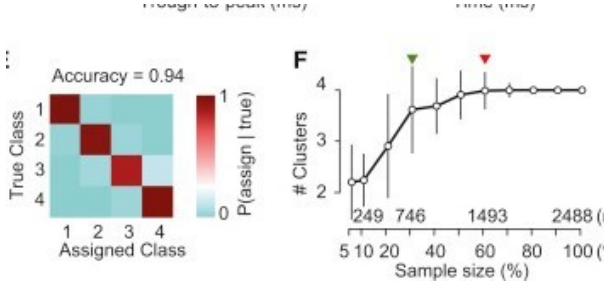


Figure 6 classification accuracy

To assess the effect of the large sample size on the number of identified clusters, they sub-sampled the data at various sub-sample sizes (100 random sub-samples for each size) and repeated the cluster analysis.(Figure 7 right)

robustness across different cortical areas

Splitting the data by areas revealed that the four classes were unequally distributed across cortical regions with different disterbution factor.

to estimate the waveform class similarity across brain regions, they quantified cross-classification accuracy between different regions.

For both cases and across all brain regions, classification accuracy was above 75%. This indicates both a consistently high separation between
the four clusters within each region and a high overlap of each cluster across regions.

In sum, the four waveform-based cell classes were robustly and similarly observed across the three cortical regions.

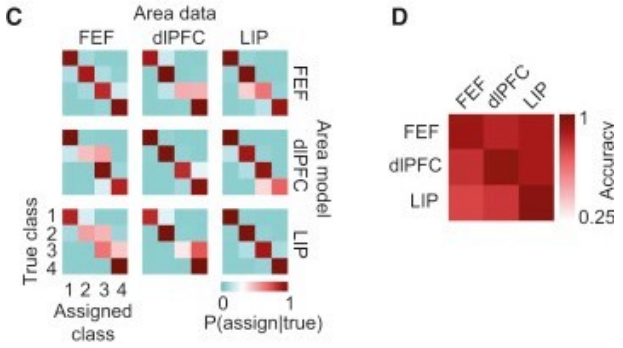


Figure 9four clusters within each region and classification accuracy

Firing Statistics of Cell Classes

If the four spike-waveform clusters reflect distinct physiological cell types, the

corresponding units should show different functional characteristics

For each neuron, they computed four statistics during this trial period: mean firing rate (FR) across trials, Fano factor (variance over mean of spike counts across trials; FF), coefficient of variation of the inter-spike interval distribution (CVISI), and burst index (BI).

During this procedure ,they found that these factor was not equal for each Cell Classes and their variation as follows:

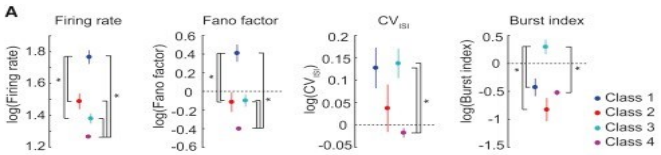


Figure 10Cell Classes vs statistics factor

Cell-Class-Specific Firing Dynamics

They investigated whether the four cell classes differed in their firing dynamics in response to a sensory stimulus.

they computed peristimulus time histograms (PSTHs) in a window including the baseline fixation period (0.5 s) and the subsequent cue period (1 s).

The cell-class-specific PSTHs pooled across regions suggested differences of the response dynamics between cell classes

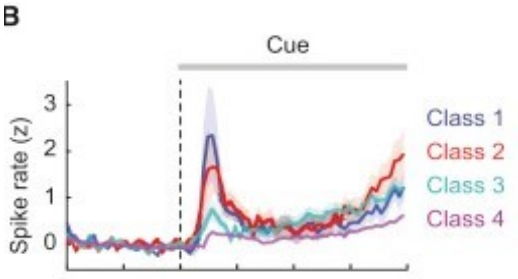


Figure 11the response dynamics between cell classes

To statistically assess this in an efficient way, they captured the firing dynamics in a low-dimensional space. They performed a principal component analysis (PCA) of the PSTHs of all neurons pooled across regions.

They estimate the effective rank of the dataset, i.e., the number of underlying orthogonal dynamical features or principal components. They found four significant components,that is same as classification Based on Spike Waveform results.

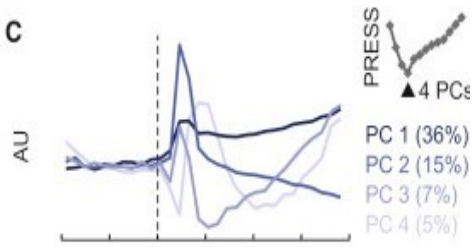


Figure 12 Four significant principal components (PCs)

explaining the PSTH variance across cell classes.

Averaging the PSTHs of all units within each brain region revealed different response dynamics across regions

Thus, they hypothesizedthatcell-class-specificresponsedynamics would be area specific.

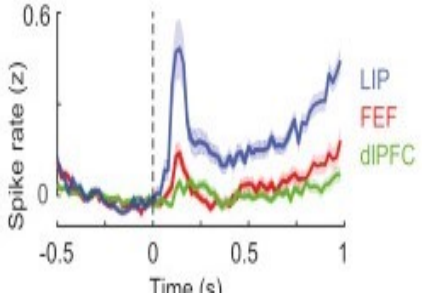


Figure 13Average PSTHs for the units recorded within each of the three brain areas

Specificity of Functional Properties

Having established that the four cell classes differ in baseline activity, response dynamics, and information coding, we pooled together all three feature sets to construct an ‘‘omnibus’’ decoder
that could predict all cell classes well .(mean accuracy 0.49).

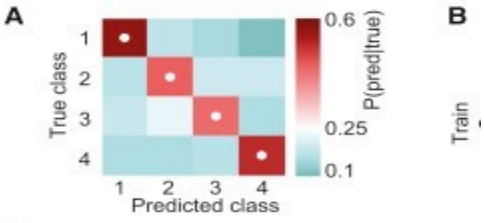


Figure 14predict of cell classes with all functional property

We computed feature importance for each of the six pairwise cell
classifications .

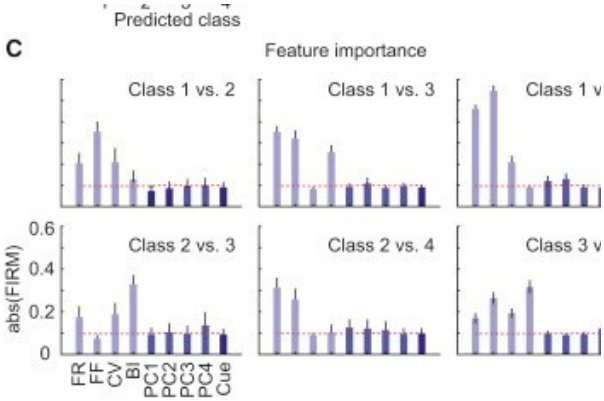


Figure 15Feature importance for all features derived from pairwise linear classifiers

then averaged to show the overall weightings .

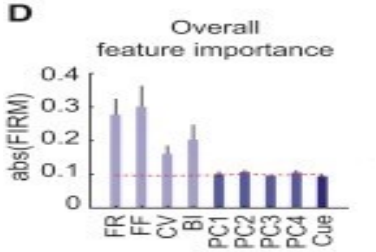
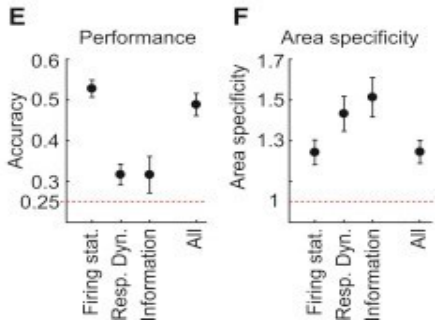


Figure 16Feature importance for all features, averaged across the six pairwise binary

Furthermore, they compared cell-class classification accuracy and area specificity for each individual feature set and all combined sets.



Finally they performed two control analyses to rule out
potential confounds,first they show that, sorting quality had not systematic difference effects on four cell classes.

Second, they ruled out that the results merely reflected different
spike waveforms or functional cell properties for the two monkeys rather than distinct cell classes.

To this end, they independently repeated the cell-class decoding for each of the two animals using all functional measures .This revealed very similar independent results for both animals mean accuracy monkey P, 0.48 mean accuracy monkey R, 0.44).

Main results

These analyses showed that cell classes were most strongly
separable by the four baseline firing statistics. This separation
was most consistent across cortical regions.

Conclusions

They show that four functionally distinct neuronal cell classes can be robustly identified from the spike waveform of extracellular recordings across several cortical regions of awake behaving monkeys.
Furthermore, this group functionally dissociating four waveform-based cell classes critically extends previous studies that dissociated only two cell classes based on extracellular recordings (narrow and broad spiking)

Refrences

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