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学位論文題目	Online spectral classification for long-term spike sorting (長時間スパイク同定のためのオンラインスペクトラル分類)

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論文の内容の要旨
Abstract of thesis

In this doctoral dissertation, Kotaro Sakamoto describes a novel method to classify extracellularly recorded action potentials or spikes addressing a long-standing issue in functional neurobiology.
The summary is as follows:

Purpose:

Action potentials are the final output of neural activity. As such, the description of the pattern of action potentials, or spikes, of individual neurons allows the precise assessment of their role in the processing of information in a nervous system. It is therefore critical to be able to faithfully record the spiking activity of individual neurons during relevant behavior.

In the mammalian brain spikes can be recorded in the close vicinity of implanted microelectrodes, mostly fabricated from fine metal wire. Increasingly, implants manufactured from silicon, which allows large numbers of recordings sites in a single implantable device, are being used. Greatly increasing the amount of data recorded and the necessity for efficient processes for spike sorting.

The action potential produced by a given neuron is highly stereotypical and its aspects are stable over the lifetime of the neuron. The shape of the extracellularly recorded spike, however, is highly variable, predominantly dependent on the spatial relationship between the recording electrode and the neuron producing the spike. This variability of the extracellular spike waveform allows the grouping of action potentials recorded from simultaneously recorded neurons (multi-unit activity) and the assignment of different spikes to their neuron of origin (single unit activity). Even in blind extracellular recordings the contribution of individual neuron to an observed activity pattern can be precisely established in good

recording conditions.

In longer recordings especially from freely behaving animals the spatial relationship between the implanted electrodes and the recorded neurons rarely remains stable over more than a few hours. Even small movements of the recording electrodes cause changes in the shape of the extracellularly recorded spikes. Since the shape of these spikes is the main criterion by which spikes are sorted, or clustered, methods have to be established to follow the activity of individual neurons even if the spike waveform changes over time.

Materials and Methods:

The author has developed a novel computational approach to solving the problem of long-term spike sorting. Two datasets were obtained in collaboration with research groups at the University of Tsukuba, both from extracellular recordings of cortical neurons in mouse cortex. The need for long-term spike sorting arose from the fact that neurons had to be observed over several wake-sleep cycles in mice to study their contribution to wake and sleep activity, respectively. Both datasets initially underwent spike sorting by trained researchers using established methods for short recordings, where little drift is expected. However, direct application of these spike sorting methods to the entire dataset (representing many hours of recordings) revealed strong changes in the action potential waveform precluding the use of established methods for spike sorting.

The author batched datasets from the long-term recordings into sliding time windows and solved Laplacian eigenproblems for each batch using the result from the prior batch as starting point. He then used k-nearest neighbor algorithm to classify the datapoints into clusters. These clusters then represent the spikes that are associated with a given neuron during the window of observation.

Alternatives for the dimensionality reduction such as locality preserving projections, uniform manifold approximation and projection and neural networks were also investigated.

Results:

Compared to manual clustering of short recordings, the approach was comparable to the output of a trained expert, using established methods. The main quality criteria are cluster distances and the potential overlap of activity. After the firing of an action potential neurons enter a refractory period of at least one millisecond. Thus, spikes with overlapping activity (intervals lower than one millisecond) represent spike sorting artefacts. This initial spike sorting comparison provided an important quality control for the computational approach.

Using the output of the classification algorithm of the prior time window as a starting guess for the next time window significantly improved the performance of the method by shortening the number of iterations needed to find the next stable solution.

The program was able to cluster the entire dataset according to established quality criteria without further human input. Greatly reducing the burden on the experimenter.

The program, which was developed in Matlab is efficient, allowing the overnight classification of millions of spikes representing many hours of recorded data, on a modern laptop computer (i5 2.3GHz CPU, 16 GB RAM). The relatively modest hardware requirements improve the applicability of the method.

Discussion:

The author notes an increasing availability of high-density recording electrodes (e.g. the neuropixel with over 1000 recording sites) and increasing demand for long term recordings. Therefore, efficient approaches that can be used to spike sort the expected large datasets have to be found.

Compared with existing approaches the quality of the established clusters is comparable and the need

for human input greatly reduced. Further quality control mechanisms based on biological criteria (e.g. known effects of neuron-neuron interactions) still need to be implemented and may further improve the quality of the process.

審査の結果の要旨
Abstract of assessment result

（批評　General Comments）

The author's approach is innovative and highly applicable to datasets form different recording techniques. The quality of the automated spike sorting process was equal to manual spike sorting by trained experts, thus achieving the same results with far less user input. The efficiency of the algorithm is such that even on readily available hardware the required computation time is a few hours, allowing researchers to spike sort an entire dataset overnight.

（最終試験の結果　Assessment）

The final examination committee conducted a meeting as final examination on January 29 2021. The applicant provided an overview of his dissertation work and addressed questions from the committee members in a subsequent Q&A session. Based on the presentation of his results and the Q&A session, all of the committee members reached the final decision that the applicant has passed the final examination.

（結論　Conclusion）

The final examination committee approved unanimously that the applicant is qualified to be awarded Doctor of Philosophy in Human Biology.