Developing and Implementing a Closed-Loop Sharp Wave Ripple Detection and Stimulation Algorithm in the CA3 Hippocampal Subregion

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Abstract

This research project aims to implement a closed-loop sharp wave ripple (SWR) detection and stimulation algorithm to detect the SWRs in rats' hippocampal CA3 subregion. SWR is a type of event-related signals that are approximately 150-250Hz, and 100ms in length. They are mainly found in the hippocampus. These signals are believed to be the signal that relates to memory replay and route planning when rats are doing a spatial memory task (Foster, D. J., 2006). These signals are hard to detect and deal with online due to the short duration, but its high amplitude and limited frequency range made it possible to be detected and interrupted during the experiment.

We developed and tested a closed-loop SWR detection and stimulation algorithm based on the Neuralynx Digital Lynx SX electrophysiology system. We've used a FIR filter to left out the 150-250 Hz signals, and checked the signal amplitude (3 standard deviations from mean) to decide if it is a valid SWR signal or not. The system can detect SWR in 4 channels. We then validate the system's accuracy and detection speed based on data from recorded rats.

The SWR detection algorithm detects the signals within 15 ms and interrupts the signals within 1ms in average. The algorithm detects and stimulates more than 99% of the SWR signals correctly and less than 1% signals incorrectly in a previously recorded dataset, showing a good performance in sharp wave ripple detection and stimulation.

By building up the detection algorithm, we can look into the question whether CA3 the hippocampal subregion that generates the SWR signals. We can also expand the use of this algorithm to experiments on other electrophysiological signals in other brain regions that has a short existing time.

Introduction

Awake SWRs were found to be related to reverse replay of behavioral sequences by David J. Foster (2006). The single-cell recording study suggests that the SWRs recorded in the hippocampus is the reverse replay of the place cell sequence that fired previously when the rat is doing a behavioral task. A research done by Girardeau later suggests that suppressing the hippocampal ripples harms the rats' spatial memory task performance significantly, showing the importance of SWRs in rats' spatial memory functions. A further research suggests that the awake hippocampal SWRs support spatial memory by showing that stimulating SWRs cause a significant learning and performance deficit in rats (Jadhav, S. P., 2012). Additionally, a research studying the relationships between Dentate gyrus (DG) and CA3 subregion suggests that the number of neurons correlating the DG and the CA3 has a positive correlation with the number of ripples detected in a set amount of time when the rat is doing the same task (Sasaki, T., 2018).

This experiment focuses on implementing an online SWR detection and stimulation algorithm that detects and interrupts the SWR signals in rat's hippocampal CA3 subregion. The main point of this experiment is to accurately detect, stimulate the SWR signals and measure the accuracy of the program.

There are two main challenges in implementing this algorithm. The first one is the "noisy" data. For the experiment design, we are recording the local field potential (LFP) data for experiment and analysis. LFP data collects the neural activities from all the nearby cells, giving this type of recording method a good way to take detailed data from a specific brain region. But the problem it provides is also obvious --- the amplitude shift is strong and the data, though not extremely noisy, also has a lot of ripple-like signals after filtering, making it hard to maintain a good accuracy. The second problem comes from the speed of the ripple. As we've previously discussed, SWR is a type of signal that relates to spatial memory learning very well, but to properly interrupt it is very hard. SWRs' existing time of around 100ms means that it needs to be detected and interrupted in the very first few milliseconds, to stop the electrophysiological activity as soon as possible.

We've implemented a real-time, closed-loop SWR detection and stimulation algorithm using a FIR filter that keeps the signals in the150-250Hz range. Then we judge whether the signal is a SWR on each channel by calculating its amplitude, if the amplitude is 3 standard deviations larger than the mean, we say that this signal on this channel is a SWR. We decide whether a stimulation should be delivered or not based on the judging result from two channels that are planted in the CA3 region. If both channels send a stimulation request within 15ms, we decide to send a stimulation to the rat's vHC hippocampal subregion. We tested this algorithm on previous recorded data, with the stimulation function either on or off.

Method

Data Used

The data we used for testing the algorithm comes from previous recordings in the rats' hippocampus. The testing procedure was done offline without an animal. The dataset has a sampling frequency of 2000Hz.

Hardware structure

Shown in Figure 1, our experiment hardware is made up primarily by the experiment system and the stimulus hardware. The experiment system is responsible for recording the rat's LFP data and position data. The LFP data will be recorded, and if required, analyzed in the system online to proceed to further actions, and in our case, apply a FIR filter and calculate its amplitude to decide if it is a SWR signal or not. The system's decision will be transmitted to the Arduino board, and if both channels classify this signal as a SWR, a confirmation signal is transferred to the stimulator, and the rat will be stimulated. The same signal will also be transmitted to the oscilloscope for monitoring purposes.

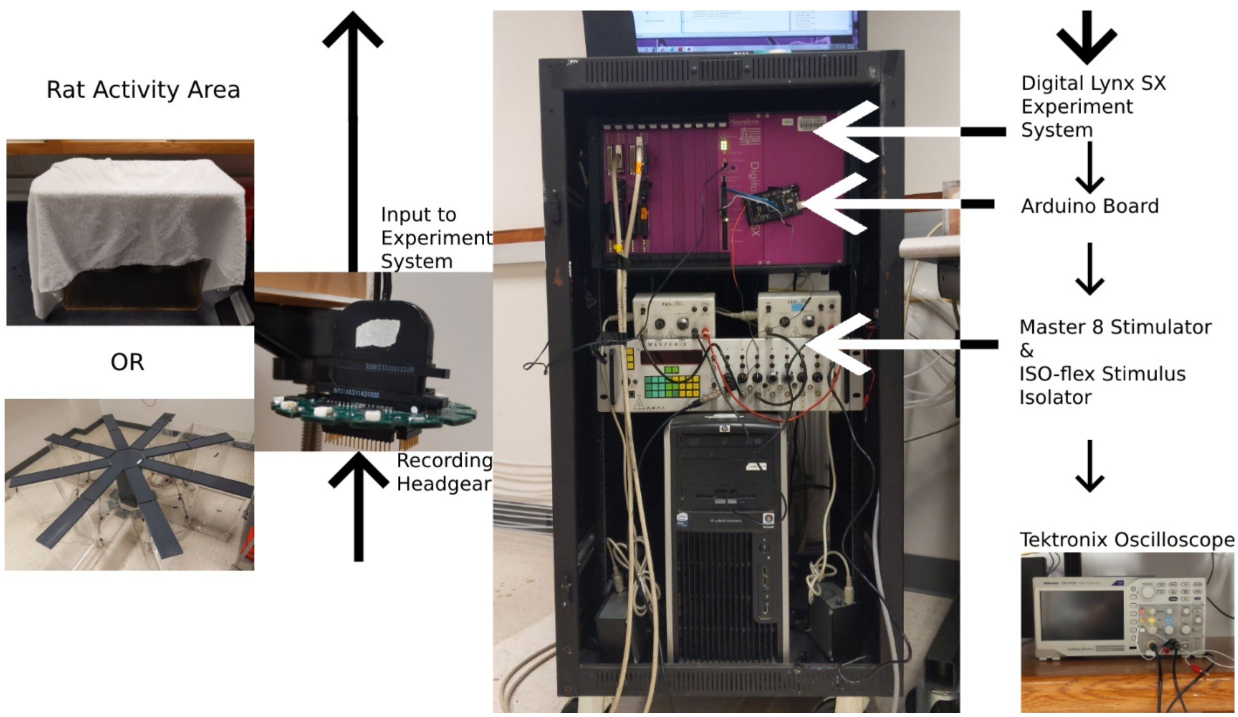

Figure 1. Closed-loop SWR detection and stimulation system. Process starts with data recording from by the recording headgear from the rat's hippocampus, goes through the recording system and stimulus system, which goes back to the rat's hippocampus.

Detection software

Stimulation methods. The SWR detection algorithm is made up of two parts. The data that gets taken into the experiment system by the recording channel goes through the FIR filter first, and then gets their amplitude calculated. If the amplitude is 3 standard deviations larger than the mean amplitude of the resting data, the stimulation signal is triggered on one channel. If two channels in the CA3 region trigger stimulation signals, the stimulation gets send to the stimulator, and stimulates the rat. After each stimulation, the system does not generate a new stimulus signal for both channels until 200ms later, to prevent extra stimulation on one SWR, or wrong stimulation, to the rats.

The FIR filter we use in the system is generated by the designfilt() function in MATLAB. It is a bandpass filter that keeps the frequency from 150Hz to 250Hz and reduces all frequencies out of this range. The left stop band frequency is 50Hz, and pass band frequency is 175Hz. The right pass band frequency is 225Hz and stop band frequency 350Hz. We set the stop band attenuation to 40, so that it doesn't constrain the frequency from 150-175Hz and 225-250Hz too much. We use the filter coefficients generated from the function directly in the filter design in our algorithm.

To get the mean and standard deviation (SD) of the baseline amplitude to compare it with the amplitude of a specific chunk of signal, we record and calculate the mean and SD value consistently through the recording and stimulating period. A threshold value will be calculated based on the mean and SD value. If any filtered signal is found to be larger than the threshold, the stimulus signal will be generated by this channel.

Since the FIR filter is not perfect, and the threshold calculation may sometimes misbehave due to extreme cases like artifacts, we want to increase the stimulation accuracy with the least time cost added possible. To solve this problem, we added 3 more stimulus detection channels. We will place all four detection channels in the CA3 region, and if two or more of the four detection channels react at the same time to a signal, we will decide that this is a SWR signal and will stimulate the rat.

EMA Power. To implement the program, we first calculate the EMA power. The EMA power is basically the power of the signal after the FIR filter. The function we use to calculate each EMA power is as follows.

$$P_t = P_{t-1} + \alpha * (|Curr\_Sample| - P_{t-1})$$

As in here, the P_t is the current EMA power, and P_{t-1} is the last calculated EMA power. Curr_Sample is the amplitude of the current data point, and the alpha value is calculated as follows.

$$\alpha = 1/(2^N)$$

The N value is the variable we will send into the program. As we can see the method looks similar as a moving average filter. And as the N gets larger, the α value gets smaller, thus calculating the power with less sudden changes. But setting a smaller N value will make the detection algorithm more sensitive to possible SWR signals. The power threshold, calculated base on the EMA power, will also change relatively.

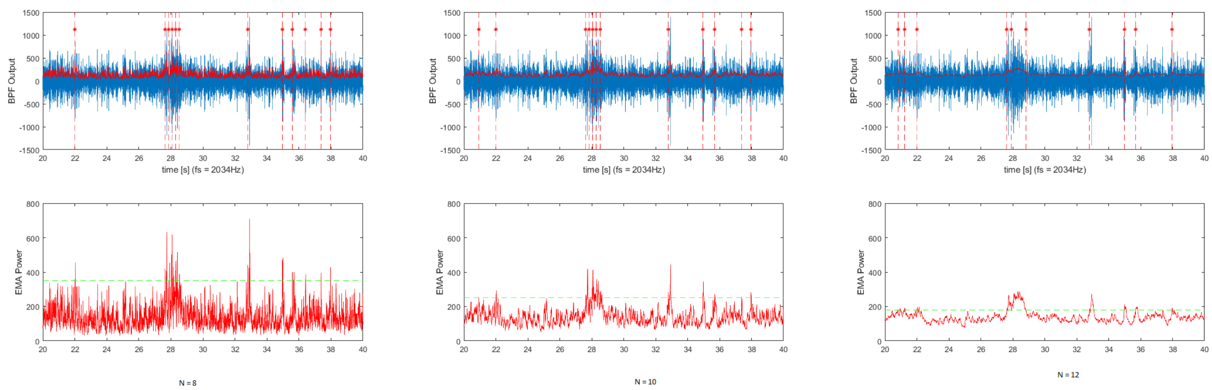

Figure 2: EMA power calculation with different N values. The upper three graphs show the signals after band pass filter, and the red lines show the SWR detection algorithm's triggering time points based on different N values. The lower three graphs show the EMA power calculation result based on three different N values. The left most result is calculated when N = 8, the middle one N = 10, the right one N = 12. To keep more details, we choose 8 as the N value.

Modifying Cutoff Frequency. When testing the algorithm, we found that the triggering results weren't working as expected. The transistor to transistor logic output (TTL) (? Or should I just say "algorithm") is triggered by low frequency, high amplitude deflection in signals, but not triggered by high frequency, high amplitude SWR event signals. The final reason was identified as the wrong cutoff frequency. The previous cutoff frequency was set to be -20dB, and that veiled some SWR signals, while taking up the low frequency deflection signals. We tried multiple frequencies, and later found that setting -40dB as the cutoff frequency is good enough for the algorithm to pick up SWR signals accurately.

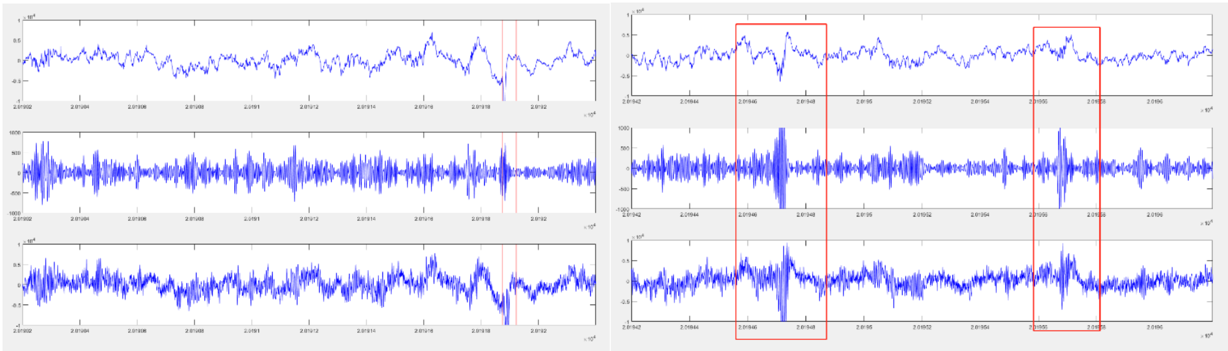

Figure 3: SWR triggering result when cutoff frequency was set to be -20dB. The red lines show the triggered SWR signal. The top graph is the original signal, the middle graph is the offline filtered signal, and the bottom graph is the online filtered signal. Red lines indicate SWR triggering. Left: SWR detection algorithm triggered by downward deflections. Right: SWR detection algorithm not triggered by SWR signals shown in the red frame.

Comparing filters / Improving Filter Latency. Through solving the mistargeting problem, we realized that the filters might be wrong. Filter 1, the first version of our filter, has been found to have unwanted filtering results, which results in providing completely incorrect SWR detection results. After using MATLAB's designfilt() function, we used and tested filter 2. Filter 2 has 553 coefficients, and is a bandpass filter from 150-250Hz. The filter is then tested by previously recorded signals from the CA3 region that contains SWR signals. Results shown that the filtered signals can be used to detect SWR signals. Figure 4 shows the impulse response of the three filters we use,

However, when testing the filter latency, we found out that this filter has a delay for approximately 15ms, as shown in figure 5. Even though the filter has a stable performance, 15ms is a long delay for a 100ms sharp wave signal. So, we decided to work on improving the filter latency. The shorter filter that we generated was found to be working as accurate as the previous filter. The filter delay also decreased to only 5ms later from the original signal, which improves the total reaction speed to SWR signals.

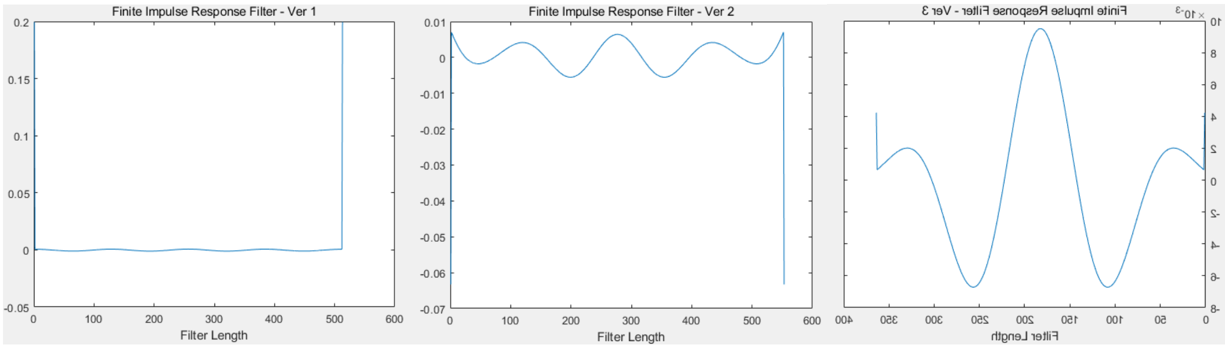

Figure 4: Impulse response of filter 1 (one on the left, x scaling from -0.05 to 0.2, 513 coefficients), filter 2 (one in the middle, x scaling from -0.07 to 0.01, 553 coefficients), filter 3 (one on the right, x scaling from -0.08 to 0.01, 364 coefficients)

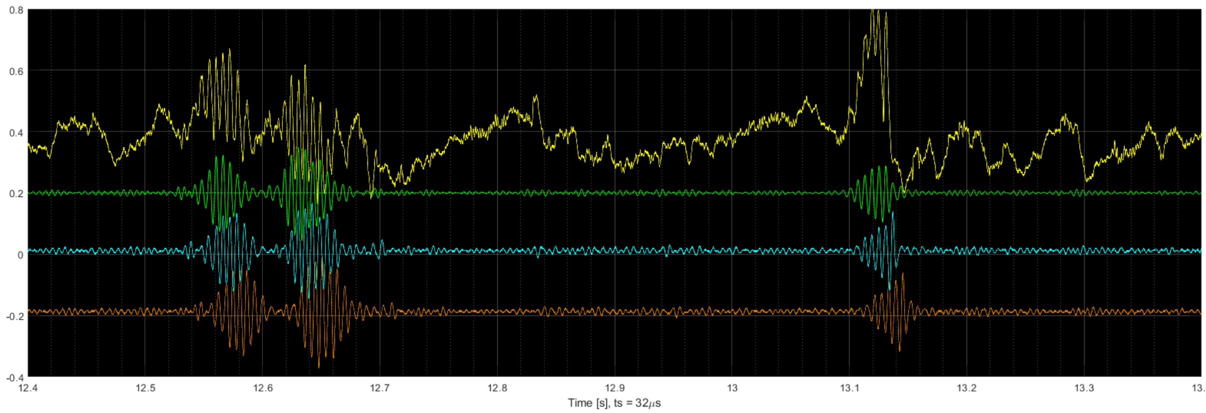

Figure 5: Comparison between original signal (yellow line), 3rd order offline Butterworth IIR filter (fs=2kHz) (green line), filter 4 (364 coefficient filter) (blue line), and filter 3 (909 coefficient filter) (orange line). X axis is time in seconds.

Result

We used a dataset previously recorded from a rat's hippocampal CA3 region to verify our results. The dataset has a recording frequency of 2000Hz, with two channels implanted in the CA3 region. We are using the most current version of our algorithm to verify the results. A subset of the data that worth 300 seconds was verified by person. We attempt to record four types of data in the validation. A "Correct stimulation" means that the two channels in CA3 both agree on one signal within 15ms that it is a SWR, and a stimulation signal is generated. A "wrong stimulation" means that although both (CA3) channels detected a SWR, it is in fact not a valid SWR signal, and it could be but not limited to downward deflection signals or motion artifacts. A "Correct single channel stimulation decision" mean that only 1 channel is triggered to a SWR signal while there actually isn't, and the other channel either didn't respond or responds more than 15ms later(It's usually the case that the other channel responds 100ms later). A "Incorrect single channel stimulation decision" means that only one channel is triggered to an existing SWR signal, while the other channel either didn't respond, or responds later than 15ms.

We recorded the number of triggers according to the following rules: If two signals from two channels respond together within 15ms, they are together recorded as one triggering signal, and is considered as a correct stimulation. If the time gap between two signals is larger than 15ms (meaning they didn't trigger a stimulus), but smaller than 200ms, they are considered as one triggering signal, and if the signal is not a SWR, this trigger is considered as a "Correct single channel stimulation decision". Similarly, if only one channel responds to a signal and the other one doesn't, it will also be considered as one single "Correct single channel stimulation decision".

The results were very positive. In 581 attempted triggering signals from the 300-second data, 282 signals are categorized as a "Correct stimulation", and the rest 299 signals are categorized as "Correct single channel stimulation decision". There are no currently recorded "wrong stimulations" or "Incorrect single channel stimulation decisions".

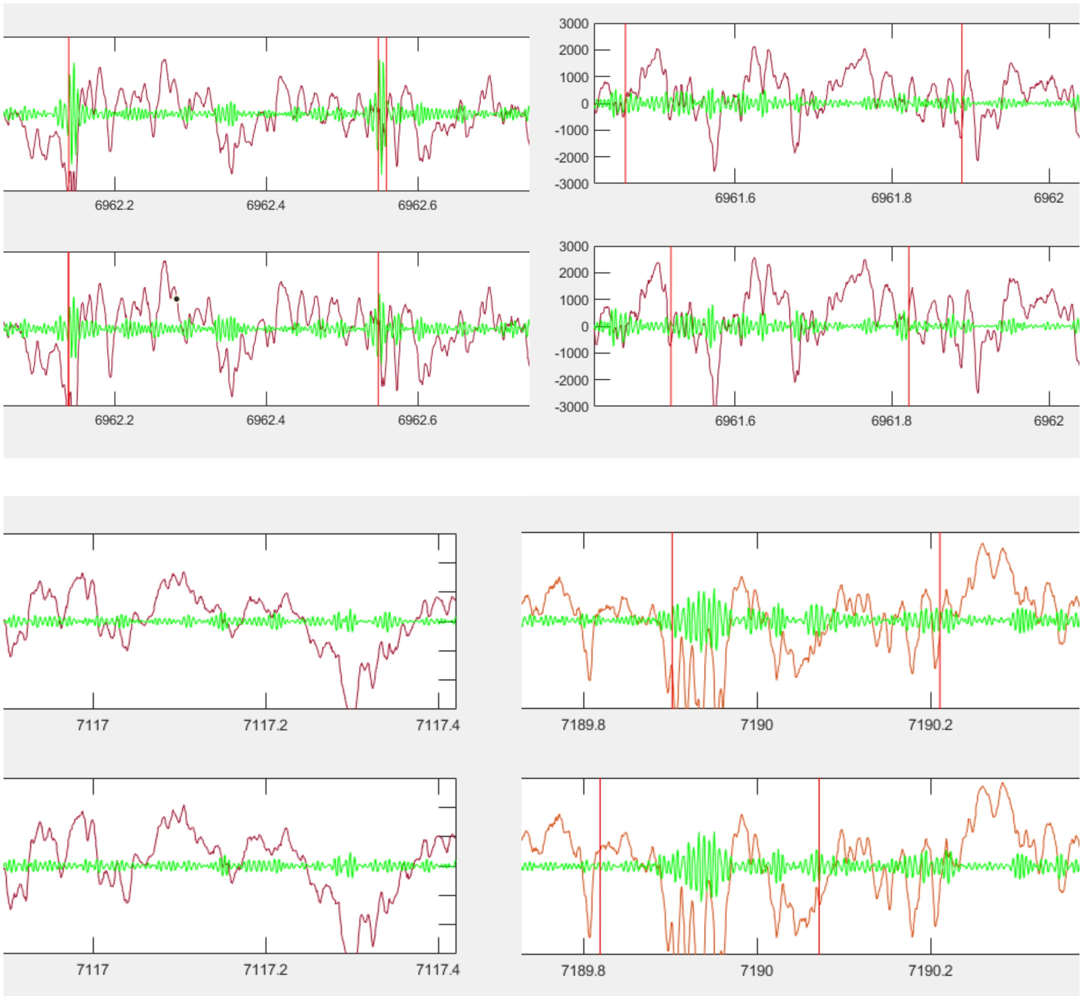

Figure 6: Separate demonstration of the detection algorithm's effects. For all four pictures, the red vertical line is the time point when one channel's detection algorithm is triggered. The green signals are the offline band-pass filtered signals, and the signals with larger amplitude are the recorded signals. The top-left graph shows an example of a "Correct stimulation". The top-right graph shows an example of a "Correct single channel stimulation decision". The bottom-left and bottom right graph shows that the algorithm works steadily when there are extreme cases in the signals (downward deflecting signals on the left, and huge unwanted signals on the right).

Discussion

We can give the credit of this good result to the following reasons. First of all, SWR signal itself is a very salient signal. It has a very steady and distinct signal feature from all other signals. Its frequency is in the 150-250Hz range, appears for around 100ms, and has an amplitude which is at least 3 times standard deviation larger than the overall signal amplitude. This makes itself a relatively easier signal to detect and interrupt on. With the filter correctly tuned and the detection algorithm calculating the correct values, the results are likely to be good.

The are still possible future improvements that can be done. Instead of a more algorithmic level, these improvements are more towards the user interaction side. Although the 200ms lockout period prevented any possible mis-triggering, it is still possibly too long, and may make us loss some SWRs that potentially appear together with each other. In that case, we want to tweak our algorithm to the point that it is able to separate two ripple signals in the range of 150-250Hz and stimulate them separately.

Making the detection channels able to set by human users is also something important to work on. The algorithm currently only fixes 4 detection channels on the Neuralynx machine, and that's not wanted in the long term as for during the experiment, some rats may not have any of those four channels implanted in the CA3 region. In that case, resetting the detection channels will be something good to have.

We would also like to know the reason why the 'single channel stimulation" happens. They are not causing troubles as they're not generating wrong stimulations, but the reason why these triggers appear is also a problem that should be better taken care of. These triggers appear at places where some signals in the 150-250Hz region do appear, but have an amplitude way smaller than a SWR. Lowering the FIR cutoff threshold may solve the problem, but may also create more false negatives. A balance point needs to be found between the amount of correct triggers and single channel triggers.

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