SPIKES FROM COMPOUND ACTION POTENTIALS IN SIMULATED MICROELECTRODE RECORDINGS.

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ABSTRACT

In this paper we demonstrate by simulation, that the spike features apparent in low-impedance deep brain stimulation (DBS) targeting microelectrode recordings (MER) may not reflect the action potentials of individual neurons. Rather, they are more likely to be compound action potentials from a synchronized group of neurons local to the electrode. Initially we simulate the MER by combining the electric fields from a large number of independent neurons surrounding the microelectrode tip. When synchronization is introduced amongst neurons the resulting discernible spikes in an MER are far more likely to relate to compound action potentials from subsets of synchronized neurons than individual action potentials. Different sub-sets of neurons are then synchronized to see how well a conventional spike sorting algorithm can differentiate the compound action potentials from different groups of neurons. These simulations offer insight into the clinical interpretation of DBS MERs used to target deep brain structures.

Index Terms— MER, DBS, point process, synchronization

1. INTRODUCTION

During the treatment of Parkinson's Disease with deep brain stimulation (DBS) a microelectrode is used to confirm the target location, e.g. the Subthalamic Nucleus (STN), in the brain. This electrode is used to both stimulate and record neuronal activity. A design consequence of using the recording electrode for stimulation is that it has a $50\mu m$ tip to increase the volume of stimulation and to prevent neuronal damage by minimizing the current density around the electrode tip. A typical MER consists of a baseline noise component and features, larger in amplitude than the noise, often referred to as spikes. These spikes are commonly interpreted as action potentials (APs) from single neurons [1, 2, 3, 4]. Characteristics of the microelectrode recording (MER), such as an increase in the noise amplitude when entering the STN, are used by the surgical team to locate the target for stimulation [5, 6].

Previous work has modeled how an increase in MER noise can be attributed to neural structure, showing that the electric field from a large number of neurons, up to 10,000 neurons, can contribute to the recording [7, 8]. In these models each neuron is simulated as a filtered point process with independent identically distributed inter-spike interval (ISI) times. As these neurons are also modelled independent from one another, there is no synchronous activity, other than by chance. These models are not representative of the STN. Studies have shown that there can be up to 25% of cells are involved in synchronous activity in the STN [5].
In this paper we demonstrate that synchronization of neuronal firing times can produce spikes in an MER known as compound action potentials (CAPs). This paper has the following structure: The methods section describes how synchronization is added to the simulation. The results section details the properties of these spikes under different conditions. The discussion section is focused on the analysis of two different synchronization mechanisms, their plausibility and the implication of these results to spike sorting of MERs from DBS. The final section summarizes the conclusions of this study.

2. METHODS

The model used in this paper is an extension of the work presented in [7, 8]. For each neuron the ISI times are drawn from the same Weibull distribution, with a shape parameter of 0.8 and a mean firing rate of $10Hz$. These parameters match the values found for a STN given in [8]. A subset of synchronized neurons are defined at random during the initialization of the simulation. An additional point process time series is generated, using a Poisson distribution for ISI of synchronized firing running in parallel. A Poisson distribution is chosen so that the synchronized events are independent and evenly distributed in time (it is not biologically based). At the spike times of this second point process a spike is added to the subset of neurons selected to be synchronized. If a neuron fires as part of a synchronized subset, the next firing time is reset and redrawn from the single neuron ISI distribution. The neuronal spike trains produced are coupled to the modeled electrode using the extracellular filtering model in [8].

In order to generate another synchronized neural sub-set the same process can be used, with a different group of neurons selected and a separate probability distribution for synchronized timing events generated. Neurons that synchronize in one group can still synchronize in another group. For spatial localization of groups, the neurons are selected using a Gaussian distribution in space centered on the group with a standard deviation based on the spatial spread of the desired group as shown in Figure 2.

The signal to noise ratio (SNR) of the spikes is calculated by taking the average maximum peak amplitude for a spike and comparing

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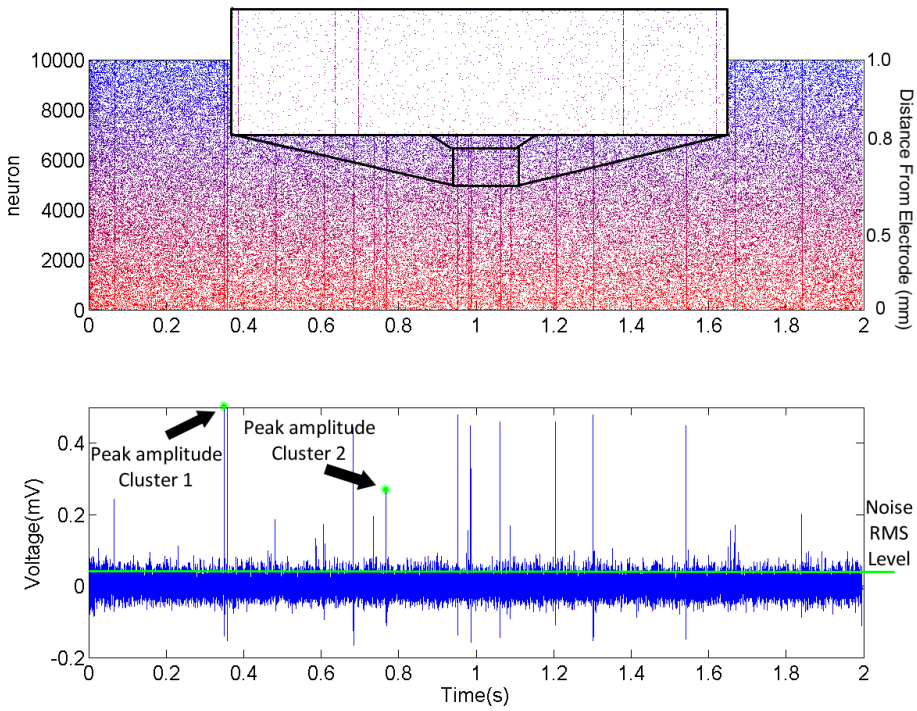

Fig. 1. Raster plot of the simulated neuron firing times and the MER time series. The vertical lines of increased density in the raster plot correspond to the synchronized firing events, with a fraction of 0.15 synchronization. There are two synchronized subsets of neurons, giving two different spike shapes/amplitudes.

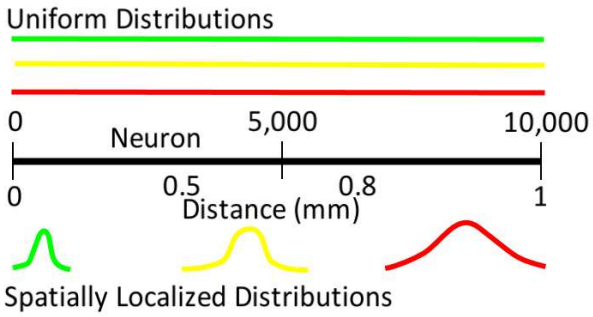

Fig. 2. Comparison of the probability of a neuron belonging to a synchronized subset for uniform distributed and spatially localized selections. The three coloured lines represent three different synchronized subsets (above the graph uniformly distributed and below spatially localized).

it to the root mean square (RMS) voltage of the noise (shown in Figure 1). Spike sorting of the recordings is performed using Osort [9], with compact support bi-orthogonal '1.5' wavelet at individual wavelet scales corresponding to between 0.1 and 1ms. The clustering is unsupervised, with cluster validity checked by comparing spike timing to the synchronized times in the simulation.

3. RESULTS

A raster plot, Figure 1, of the simulated neuron firings shows how the synchronized firing times correspond to a spike with a large signal to noise ratio. In the raster plot two separate synchronized subsets can be seen. Although there are two subsets with the same percentage of total neurons synchronized, their spatial arrangement around the electrode are different. The effects of this spatial arrangement can be seen in the MER time series, where two different spike shapes are present.

As the number of neurons that are synchronized increases Figure 3 shows a linear increase of the mean peak amplitude of the CAP spike, averaged over 20 simulations. The variance of the peak amplitude also increases significantly, depending on the spatial distribution of the sub-set of synchronized neurons, i.e. as more neurons are synchronized they are more likely to come from a wide spread of locations. Figure 3 shows synchronization over the biologically plausible range of 0-0.30 for the STN [5]. For synchronization above 0.5 the mean peak signal amplitude becomes constant at $8.06 \pm 0.52\ mV$, with variance decreasing to zero when all neurons are synchronized.

Figure 3 shows when two sub-sets of synchronized neurons differ substantially in their spatial distribution, spike sorting can be

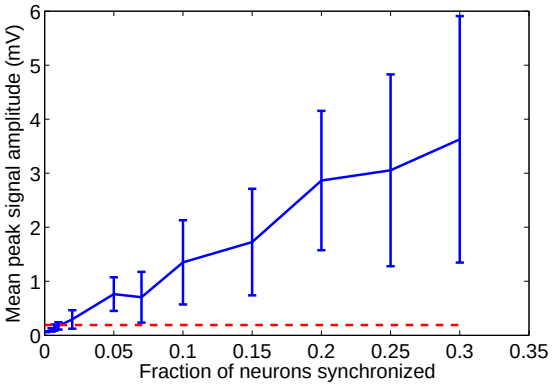

Fig. 3. Mean peak signal amplitude as the fraction of neurons in the synchronized sub-set changes. The mean is taken over 20 simulations and the error bars are one standard deviation. The dashed line represents the average RMS value of the recordings, shown in Figure 1.

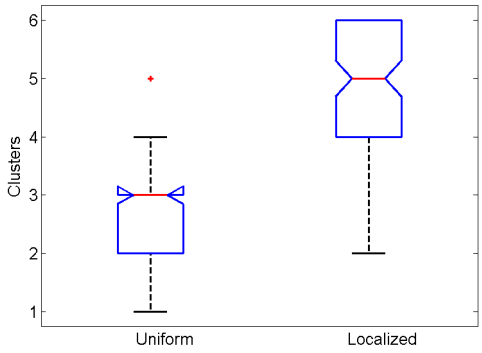

Fig. 5. The number of groups clustered for six spatially localized and six uniformly distributed subsets of synchronized groups of neurons over 100 simulations. The sticks represent the maximum and the minimum number of groups, the box represents the 25th and 75th percentile and the notch is the mean.

successfully achieved. This occurs more often when the neurons are spatially localized, however it can occur when the two sub-sets are uniformly distributed as per Figure 2.

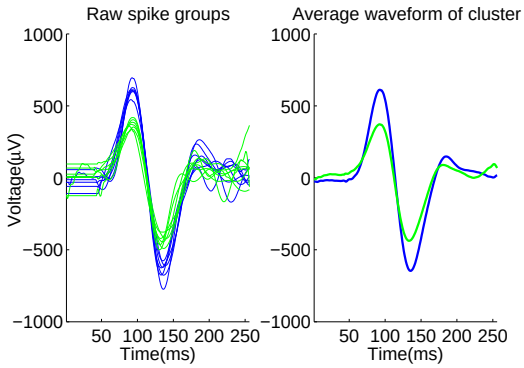

Fig. 4. Comparison of two CAPs after spike sorting from a simulation with synchronization percentage of 25% total synchronization. For this simulation there were two synchronized subsets of neurons with each subset uniformly distributed across all the neurons and 12.5% of neurons in each set.

Figure 5 shows that when the synchronization of six neural subsets is changed from uniform across space, to spatially localized, the spike sorting algorithm can distinguish more clusters. For the uniform distribution only two to three clusters are found 50% of the time. For the spatially localized neural subsets more than four clusters are found 75% of the time.

4. DISCUSSION

Figure 3 shows that for no synchronization there is a chance of having a peak signal amplitude two times above the RMS noise. In this case a neuron current source (the axon hillock) is located close enough to the electrode tip for its action potential to be significantly larger than the background noise and thus appear as a spike. This shows that it is possible for DBS MER spikes to represent single neuron activity. However, the likelihood of two or more neurons contributing AP spikes in these MER simulations is very low because of their spatial distribution.

There are two methods to produce visible spikes in the MER simulations. The first method is to place a neuron very close to the electrode (where the current source is adjacent to the tip of the electrode). The second method is to introduce synchronization and produce a CAP. For DBS MERs the spikes are often thought to be APs produced by single neurons. Spike sorting techniques, based on shape, amplitude and rate, are then used to determine if the MER spikes all correspond to the same neuron, or multiple neurons firing at different times [9]. It can be seen that these spike sorting methods can also be used to sort CAP spikes generated by synchronization, depending on the spatial distribution of the synchronization within the STN.

When synchronization was uniformly spread through the STN the spike sorting of different synchronized subsets failed to produce the correct number of clusters. This is due to the effective shape of the CAP produced by a subset of synchronized neurons being too similar. Their similarity in shape of the spike is an average effect of the action potentials from each neuron that is synchronized. As the distribution of the synchronized subsets has a uniform probability of selecting any neuron, the average spike shape for each subset is on average the same. In general the CAP shape is dominated by the closest neurons to the electrode, with minimal extracellular filtering. On average neurons that are further away are more likely to be selected because the number of neurons located at a particular distance depends on the square of the radial distance from the electrode, r^2. However, the further the neuron is from the electrode, the more the electric field is filtered by the extracellular medium [7, 8, 10, 11], with an amplitude decay larger than $1/r^2$. Therefore, the main difference between the two CAPs produced by a subset of synchronized neurons will be the total number of closer neurons, which will

change the amplitude of the spike, as seen in the example in Figure 4.

When the synchronized subsets are defined to be spatially localized, rather than across all of the STN, the compound action potentials are no longer dominated by the closest neurons. Rather they reflect the average AP at the mean spatial location of the cluster. This increases the success of the spike sorting because each CAP not only differs in amplitude but also in shape due to extracellular filtering.

A point to note from Figure 5 is that the spike sorting never overestimates the number of synchronized subsets. The low likelihood of two neurons producing AP spikes in the recording combined with this point would suggest that spatially localized synchronization is the most likely explanation for a DBS MER when the spikes can be sorted into multiple clusters. A limitation of this model is that the peak amplitude for a single neuron AP is limited in size to the minimum distance a neuron can be generated at. In practice there is no limit to the neuron-electrode distance, meaning that peak amplitude cannot be used to differentiate between spikes from CAPs and very close APs.

Simultaneous MERs can not be obtained in a target structure during a DBS surgery. The exact location of neurons around the electrode is also currently unmeasurable. These limitations, along with the spike mechanisms presented in this paper, mean that it would be unlikely to differentiate between APs, a single synchronous neuronal subset and multiple uniformly distributed synchronous neuronal subsets. Due to this complication, DBS MER spikes are most sensibly considered as an indication of the target structures overall activity. If the spikes can be sorted into multiple clusters, it indicates that there is most likely spatially localized synchronized neuronal subsets. Alternitively, the spikes can be sorted into a single group to obtain a measure of overall activity.

The method used for adding the synchronization uniformly in this paper is artificial and not based on a biological mechanism. This was chosen only to demonstrate that with synchronization, sortable spikes can emerge from the CAPs in MERs. The model was extended to include spatially localized synchronization to improve biological plausibility and making the CAPs differ in amplitude and shape. This distribution relates to the idea of somatotropic maps of the STN, which show that there is localized organization in the STN related to different movement tasks [5].

Future work will focus on increasing the biological plausibility of this model, structures external to the STN, such as the entire Basal Ganglia, can be included. These external structures can be used to control the amount of synchronization, and the statistics of the synchronized spikes. Controlling the ISI times using an external structure allows for non-stationary ISI statistics, which could be used to analyze MERs when patients are performing transient tasks.

5. CONCLUSIONS

This work shows that synchronized firing between different neurons located near a microelectrode can produce what appears to be a single neuron action potential, but is actually more likely to be a compound action potential. As the number of synchronized neurons, within a biologically plausible range, increases the signal to noise ratio for these spikes increases. Standard spike sorting methods cannot appropriately cluster spikes which occur when the neuronal synchronization is uniformly distributed. The spike sorting methods perform better when the synchronized groups are spatially localized.

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