32nd Annual International Conference of the IEEE EMBS
Buenos Aires, Argentina, August 31 - September 4, 2010

# An automated online positioning system and simulation environment for multi-electrodes in extracellular recordings

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*Abstract*— **Extracellular recordings are a key tool to record the activity of neurons in vivo. Especially in the case of experiments with behaving animals, however, the tedious procedure of electrode placement can take a considerable amount of expensive and restricted experimental time. Furthermore, due to tissue drifts and other sources of variability in the recording setup, the position of the electrodes with respect to the recorded neurons can change causing low recording quality. The contributions of this work are threefold. We introduce a quality measure for the recording position of the electrode which should be maximized during recordings and is especially suitable for the use of multi-electrodes. An automated positioning system based on this quality measure is proposed. The system is able to find favorable recording positions and adapts the electrode position smoothly to changes of the neuron positions. Finally, we evaluate the system using a new simulator for extracellular recordings based on realistically reconstructed 3D neurons.**

## I. INTRODUCTION

The use of large arrays of multi-electrodes (AME) is a popular recording technique, since it combines two favorable aspects with respect to data analysis. Namely, the temporal resolution is high enough to record spike trains of single neurons, but also the activity from a large number of neurons is captured simultaneously. While more methods become available to process, sort and analyze such large amounts of data obtained from AME recordings (see e.g. [1], [2]), only a few contributions deal with the task of properly positioning the individual multi-electrodes. When considering acute recording experiments with electrode arrays of 16 or up to 64 tetrodes, it is evident that positioning every single electrode manually becomes a time consuming part of the experiment. This is in particular an issue when carrying out experiments with primates, as maximum experiment duration is often limited by national animal protection laws. Hence, there is a need for an automatic multi-electrode positioning algorithm which would place individual electrodes not only faster and more reliable than a human, but possibly also several electrodes simultaneously, reducing considerable amount of setup time. Additionally, even when the experimenter succeeds in placing all electrodes at favorable positions at the beginning of a recording session, the signal quality can decrease during the recording. In fact, due to the insertion of electrodes, the brain tissue is compressed. During the experiment, the tissue relaxes again, which can lead to a displacement between the electrodes and the surrounding neurons [3]. Consequently, an experimenter would have to constantly monitor the recording quality of each electrode, and adapt its position in order to maintain acceptable recording performance.

In [4], [5] an autonomous electrode positioning algorithm was proposed, which was designed to isolate single neurons. We propose a method that differs in several ways from this approach. In brief, the use of tetrodes (or other multi-electrodes) allows for a superior discrimination performance of the recorded spikes, simplifying spike classification on such data as compared to data from single electrodes [6]. This is due the fact, that a spike waveform is recorded simultaneously on several recording channels (”stereo-effect”). Keeping this advantage in mind, it should be preferred to record the activity form several neurons on the same multi-electrode in order to maximize the information yield about the local neural population. Hence, we propose a quality measure which favors electrode positions where most likely several neurons are present. In contrast to the work presented in [4], [5] our method does not rely on error-prone and time consuming results of spike sorting.

To evaluate automatic positioning algorithms, simulated recordings of extracellular potentials (EP) were utilized. Compartmental membrane currents of a spiking, reconstructed L5 pyramidal cell from [7] were simulated using the simulation tool NEURON [8], [9], and subsequently used to calculate EP-traces using the line-source method [10]. In turn, a simulation environment which allows the simulation of virtual electrode movements in a volume containing many neurons and realistic noise using these traces was developed.

The remainder of this article is organized as follows. In section II the new quality measure is introduced. The positioning system that tries to maximize the quality over time is described in III. The simulator used for online use and evaluation of the system is outlined in IV and the results of the evaluation can be found in IV-C.

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Felix Franke and Klaus Obermayer are with the Bernstein Center for Computational Neuroscience Berlin, Germany and supported by DFG GRK 1589/1 and BMBF grant 01GQ0743

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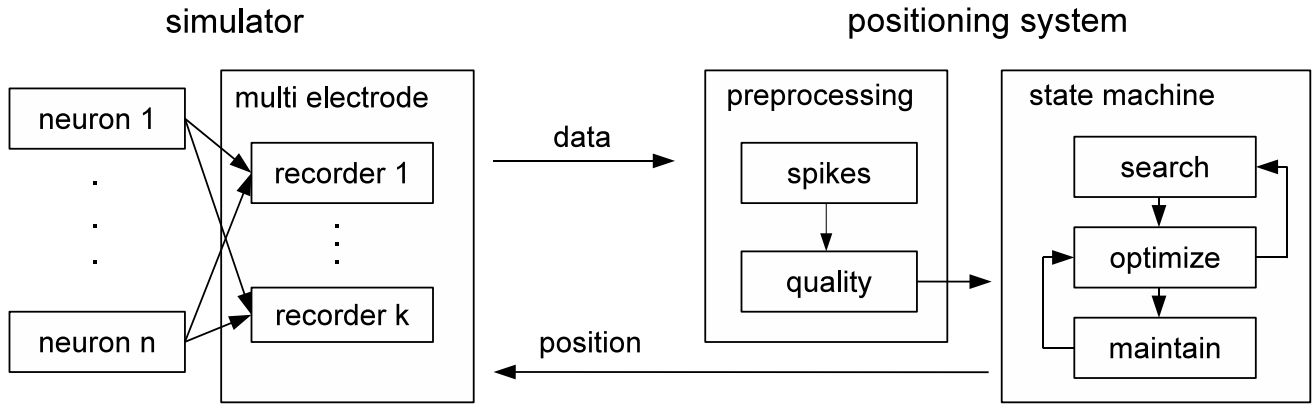


Fig. 1. Simplified overview of the complete simulation and positioning framework. Data is simulated by placing morphologically reconstructed neurons in a 3D space. Multi-electrodes that are composed of a number of recorders can record the spikes emitted by the neurons in their vicinity. The data are then passed to the positioning system. After a preprocessing step the state machine decides where to place the electrode and sends this information back to the simulator.

## II. QUALITY METRIC

### A. Problem statement

In this work we are interested in a general quality measure for the recording position of an extracellular electrode which can be used in many different experiments and does not make any further assumptions about the neurons recorded other than that they should have a minimum firing rate during the experiment. Such a quality measure $Q$ should omit possible biases to certain neuron types as much as possible. As opposed to other recording techniques where the explicit goal is to record only from one single neuron, we try to increase the total yield of recorded neurons after sorting, maximally exploiting the stereo-effect of multi-electrodes. This leads to the following constraints for the quality measure $Q$:

- Invariance to firing rate of neurons
- Maximization of the signal-to-noise ratio, the number of recorded neurons and the separability of spikes from different neurons
- Monotonic growth with parameters to be maximized
- Robustness to noise and variability of the data
- Fast computation

Especially the last two constraints restrain the use of clustering to estimate the number of neurons: Clustering procedures need considerable amounts of computation time and the problem of determining the number of clusters consistently over time would lead to abrupt changes of the quality estimated. However, we want to emphasize that the complete framework presented here can also be used unchanged with different quality measures.

### B. Definition

Let $s_k^i$ be the waveform of the $i$-th detected spike on channel $k$ and $N$ be the total number of detected spikes in a piece of data $X$ of length $T$. Let further $\sigma_k$ be the noise standard deviation at the recording channel $k$. Then, the channel wise peak-to-trough SNR of a spike with respect to the noise distribution is defined as:

$$SNR_k(\boldsymbol{s}_i) = P(\boldsymbol{s}_k^i) := \frac{max(\boldsymbol{s}_k^i) - min(\boldsymbol{s}_k^i)}{\sigma_k} \quad (1)$$

The detectability of the spikes detected during period $T$ is just their mean SNR:

$$Q^{SNR}(X) := \frac{1}{N} \sum_{i,k} P(s_k^i) \quad (2)$$

The discriminability of the spikes via the stereo effect can be approximated by the difference of their SNRs among the channels. This can be expressed by the difference of the SNR distribution of every single spike to the mean SNR distribution:

$$Q^{stereo}(X) := \frac{1}{N} \left[ \sum_{i,k} \left| \langle P_k \rangle - P(s_k^i) \right| \right], \quad (3)$$

where $\langle P_k \rangle := \frac{1}{N} \sum_i P(s_k^i)$. Both measures can be combined to a single quality measure by simply adding both terms:

$$Q(X) := \frac{1}{N} \sum_{i,k} \left[ P(s_k^i) + c \cdot \left| \langle P_k \rangle - P(s_k^i) \right| \right] \quad (4)$$

It is important to note that this quality measure is monotonically increasing with both, the theoretical SNR of single neurons and their discriminability, if $c < 1$ (see Fig.2). The maximization of the number of neurons is implicitly rewarded by $Q^{stereo}$: Only spikes from different neurons can have different discriminable stereo effects. In the top of Fig.3, an example of the quality measure calculated for different depths of a simulated electrode track is shown. Note that the function is invariant to the rate of the neurons (Fig.3, middle).

## III. POSITIONING SYSTEM

The positioning system consist of two main parts: A preprocessing of the incoming extracellular recordings and a state machine which controls the movement of the (multi-)

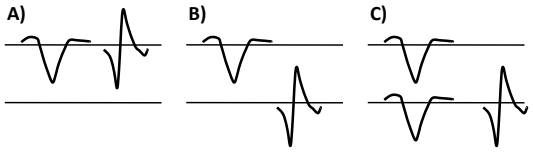


Fig. 2. Effect of spike waveform on the quality measure. *A* Both waveforms have their energy on the same channel yielding a low quality. *B* The energy of the two waveforms is unequally distributed among the channels which is rewarded by $Q^{stereo}$. *C* This combination has the highest quality, since the increase in SNR exceeds the loss in stereo effect.

electrode. A schematic overview of the system is shown in Fig.1 right.

### A. Preprocessing

In order to operate online and reasonably fast, the system analyzes small periods of recording. We assume that the data is already bandpass filtered. Spikes are detected by thresholding the squared signal. For every spike the SNR on all channels is calculated individually and the quality of the current data period evaluated. This information, together with the current electrode position is passed to the state machine.

### B. State machine

The decision logic of the positing algorithm was realized by implementing a finite state machine consisting of 4 states, see Fig. 1. The electrode stays at each position for a certain amount of time for gathering sufficient data to reliably estimate the quality measure. Depending on this value, the algorithm decides to which subsequent state the system has to transit. In the following each state is described in detail as well as its transition criteria.

*1) Search:* This is the initial state, and as long as the quality of the signal is below a certain threshold $Q_{min}$, the electrode is simply advanced in the direction $D$ ($D$ is either -1 or 1, since electrodes can be moved only in either of two directions, namely back or forth) by a constant step size $S_s$. If three consecutive quality estimates yield a value larger than $Q_{min}$, the algorithm changes to the "optimize" state.

*2) Optimize:* The goal of this state is to determine the position at which the quality function exhibits a local maximum, and hence the electrode should be moved to. The function $Q$ and its derivative $g$ are not know a priori, but only noisy observations are available, which suggests the use of methods from stochastic approximation [11]. One way to solve this would be the use of a two-sided finite difference approximation for the gradient, but despite popular use of this technique, it is inappropriate for realization in our setting. A realization of a two-sided finite difference would imply that in order to estimate the derivative, the electrode would have to move forward and backward at every position (dithering). This might damage the brain tissue and also evoke further drifts. The problem of estimating the gradient and the second derivative $g'$ can be avoided by introducing an interpolation function. In order to keep the algorithm simple we use piecewise interpolation. As interpolation functions cubic Hermite polynomials seem to be a reasonable choice (e.g. they have no overshoots or oscillations in contrast to splines). In contrast to [4], our approach avoids the task of order estimation and there is no risk of oscillations at the ends of the fitted data. The Hermite polynomials are fitted through the average quality estimates ($Q^{(k)}$, ..., $Q^{(1)}$) and the next electrode position $u^{(k+1)}$ is determined by a modified Newton-Raphson rule[1] $u_{k+1} = u_k + a_k \cdot g(u_k)/|g'(u_k)|$.

If the gradient changes sign, the last 3 qualities are interpolated with a quadratic polynomial, and the electrode is moved to the position with the highest interpolated quality value. This prevents further unnecessary oscillations (similar to dithering) of the electrodes resulting in tissue damage. Once the optimal electrode position is reached, the algorithm switches to the "maintain" state.

*3) Maintain:* The electrode stays at the best found position until the quality drops under a certain value. Explicitly, if the quality $Q$ drops below a certain absolute value, i.e. $Q < Q_{mm}$, or a certain relative value, i.e. $Q < t \cdot Q$, the "find" state is triggered. On the other hand, if there is a sudden dramatic quality drop, $Q < Q_{min}$, the algorithm returns to the "search" state.

*4) Find:* (not shown in Fig.1) In this state the algorithm moves the electrode in an arbitrary direction. If the quality is even lower than at the previous position, the direction is inverted and the algorithm switches back to the "optimize" state.

## IV. SIMULATOR

We developed an online simulator for extracellular recordings that can incorporate feedback from positioning systems (see Fig.1, left side). It consists of mainly three building blocks: Neurons, recorders and noise sources. Neurons are defined by their 3D position, orientation and their firing behavior. For every point in space a neuron has a characteristic morphology dependent waveform of their extracellular field potential (see section IV-A). A recorder is defined only by its 3D position and sampling rate. For example, a tetrode consists of four recorders with a certain spatial distribution. Every recorder simulates a recording channel. This way, arbitrary multi-electrodes can be simulated. All recorders of a multi-electrode can only be moved simultaneously. If a recorder is close enough to a spike generating neuron, the corresponding waveform of that neuron and the relative position of the recorder to the neuron will be copied into its simulated data. Every multi-electrode additionally has a noise source with a given noise covariance matrix (see section IV-B).

### A. Estimation of extracellular field potential

Extracellular field potentials around a reconstructed layer 5 pyramidal neuron were calculated using a forward electrostatic scheme similar to the line-source method described in Holt and Koch [10]. The reconstructed neuron was a cat L5 pyramidal neuron published in Mainen and Sejnowski

[1]More specifically, the Newton-Raphson method is combined with the steepest ascent method, in order to guarantee that the solution is a local maximum instead of a local minimum.

[7]. The membrane currents for each of the 1094 compartments of the reconstructed neuron were calculated using the simulation tool NEURON [8] with the Python interpreter [9], using a somatic action potential (AP) trace as a forced boundary condition in the single compartment representing soma, similar to Pettersen and Einevoll [12].

For the compartmental neuron simulation, purely passive membrane properties were assumed, with an intracellular, axial resistivity of $R_{\mathrm{a}} = 150\Omega$cm, membrane resistivity $r_{\mathrm{m}} = 30000\Omega\mathrm{cm}^2$, membrane capacitance $c_{\mathrm{m}} = 1.0\mu\mathrm{F/cm}^2$, and an initial crossmembrane potential of $v_{\mathrm{init}} = -65$V. The simulated membrane currents and the corresponding coordinates of these sources were used to estimate the EP at each time-step using the line-source method [10], with an homogenous extracellular conductivity $\sigma_{\mathrm{e}} = 0.3$S/m.

The soma, with mid-point position $\vec{r}_{\mathrm{soma}} = [0, 0, 0]$, was treated as a point source, and the contribution to the EP from the somatic membrane current $I_{\mathrm{soma}}(t)$ in coordinate $\vec{r}$ is in the quasistatic approximation to Maxwell's equations given by $\Phi(\vec{r}, t) = \frac{1}{4\pi\sigma_{\mathrm{e}}} \frac{I_{\mathrm{soma}}(t)}{|\vec{r}-\vec{r}_{\mathrm{soma}}|}$ . The analytical solution to the linearly super-positioned potential from $n$ segments, where $I_k(t)$ is the membrane current of segment $k$, is given by [13];

$$\Phi(\vec{r}, t) = \sum_{k=1}^{n} \frac{I_k(t)}{4\pi\sigma_{\mathrm{e}}\Delta s_k} \log \left| \frac{\sqrt{h_k^2 + \rho_k^2} - h_k}{\sqrt{l_k^2 + \rho_k^2} - l_k} \right| , \quad (5)$$

where $\Delta s_k$ is the segment length, $\rho_k$ the distance perpendicular to the axis of the line-source, $h_k$ the longitudal distance to the end-point of the segment, and $l_k = \Delta s_k + h_k$ the longitudal distance from the start-point of the segment [12], [13]. The calculations of EPs were done during the same simulations as the NEURON simulations, still using the Python interpreter.

In order to avoid singularities in the EP when the distance to individual segments was small, the minimum allowable distance to each line source was set to be the same as the diameter of each segment. This also ensured that the potential is not calculated within the intracellular space of the chosen morphology. The calculation of the EP was performed over the coordinates of 3D cubic grids spanning [-200, 200]$\mu$m and [-100, 100]$\mu$m, with spatial resolutions of 5 and 10 $\mu$m respectively, sampling the extracellular signature of the AP in the volume surrounding the somatic compartment and basal dendrites. The calculation of potentials at larger distances was not deemed necessary due to the low resulting extracellular amplitudes compared to the noise added at a later point. The resulting potential traces and corresponding coordinates were written to file on the HDF5-format, and then used by the extracellular recordings-simulator.

### B. Noise

Noise was simulated with a multivariate autoregressive model (AR) of order 12. First, the noise covariance matrix of spike free periods of tetrode recordings from macaque prefrontal cortex [2] was estimated. Then, the AR model was fit with a Python implementation of [14] and subsequently used for the generation of noise.

### C. Simulation parameters

For the evaluation of the positioning system we used an artificial neural environment consisting of 16 simulated and randomly oriented neurons. A tetrode was simulated having the four electrodes at the corners of a tetrahedron (the electrode tip had a distance of 40$\mu$m to the other three electrodes which had a distance of 20$\mu$m to each other. It could be freely moved along a one dimensional track (see Fig.3, bottom plot, dotted line). The neurons were placed in a way that 3 possible favorable recording positions are present on the track corresponding to three clusters of neurons (A, B and C respectively). The neurons in cluster A and C had the same relative positions. The mean distance of the neurons to the recording track were smallest for cluster B, giving this cluster the highest SNR. Within each cluster all neurons had the same firing rate (15Hz, 7Hz, 5Hz respectively). The empirically estimated firing rate at the tetrode using a threshold (4 times the standard deviation) spike detector on the absolute signal is shown below. Note that the quality is independent of the firing rate. A piece of simulated data is shown for four different recording positions corresponding to noise and positions within the 3 clusters (Fig.3, bottom). Fig.3 top shows the quality measure for different electrode depths, whereas a value of $c = 0.95$ was chosen, see (4). The quality was estimated by systematically moving the electrode in 15$\mu$m intervals along the track recording for 2.5 seconds at each position.

The positioning system was then used to find favorable recording positions. Depending on the experimenters choice for parameter $Q_{min}$ the "optimize" state will be triggered either for recording position A ($Q_{min} < 29$) or position B ($30 < Q_{min} < 40$) and finds the corresponding local maximum.

## V. DISCUSSION, CONCLUSIONS AND FUTURE WORKS

### A. Discussion

The problem of assigning a distinct quality to a certain recording position is a peculiar one since the chosen position will affect all further analysis of the recorded data. This means that if the quality is defined in a way that biases the positioning system towards e.g. fast spiking neuron types, all recordings will suffer from and the results inherit this bias. It turns out that it is indeed extremely difficult - if not impossible - to define an unbiased quality metric, especially since we do not know the true nature of the surrounding network. However, this is not necessarily an argument against automated positioning systems. If humans are controlling the system they can also be seen as a part of it - having a certain quality metric even though it is only implicitly defined by the experience of the human operator. Therefore, we argue for the importance of explicitly stating and documenting this metric in the experimental protocol. Only then the kind of bias one can expect will be known and can be used to re-evaluate certain aspects of the experiment after more facts about the true nature of neural firing behavior are known.

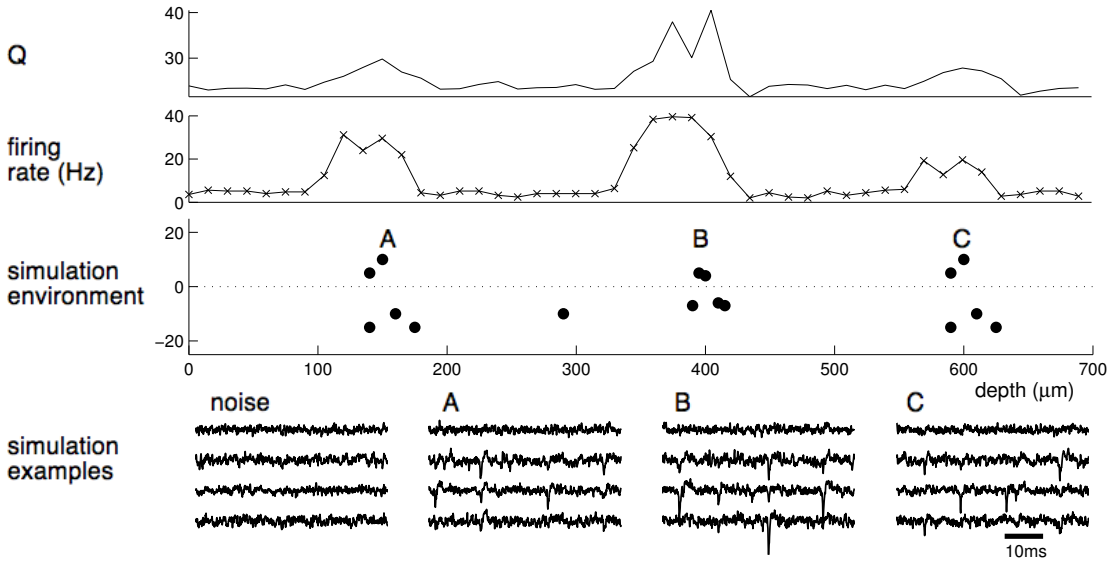


Fig. 3. Simulated recording environment containing 16 neurons (black dots) in 3 clusters (A,B and C). The dotted line represents the track of a simulated tetrode. Also shown are the empirically estimated firing rate (middle) and the quality (top) of the corresponding recording positions. Details see text (IV-C). For four of the positions ($0\mu m$, $150\mu m$, $400\mu m$ and $600\mu m$) short pieces of simulated data are shown (bottom).

### B. Conclusions

We proposed a new quality measure for the recording position of multi-electrodes in extracellular recordings. This measure was combined with an adaptive online positioning system that can thus automatically find and maintain favorable positions. The basic functionality of the system was demonstrated with the use of a new simulation environment for extracellular recordings based on realistically reconstructed 3D neuron morphologies. The complete framework was written in Python and we hope that it can be used to foster the development of spike detection and sorting algorithms as well as automated positioning systems. Due to the fact, that the extracellular waveforms are calculated before the actual simulation, the environment runs extremely fast, allowing a large number of simultaneously simulated neurons and recorders.

### C. Future Works

There are many possible ways to define the quality of a certain recording position, e.g., more sophisticated measures of cluster separability of the detected spikes could be used. That choice will depend on the experimental context.

Another issue are tissue/electrode drifts. These have to be detected and the position adopted accordingly. At the moment this will happen, if the quality of the current recording position drops under a certain threshold. However, the stereo effect of tetrodes could be used to triangulate neurons and estimate the direction and speed of the actual drift to optimally counteract it before the quality drops.

The next step in evaluating the system will be the simulation of electrode/tissue drifts and the operation of the system in a real experiment.

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