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Theoretical analysis of intracortical microelectrode recordings

Scott F Lempka^{1,2}, Matthew D Johnson³, Michael A Moffitt⁴, Kevin J Otto⁵, Daryl R Kipke⁶, and Cameron C McIntyre^{1,2}

¹Department of Biomedical Engineering Cleveland Clinic Foundation, Cleveland, OH, U.S.A

²Department of Biomedical Engineering Case Western Reserve University, Cleveland, OH, U.S.A

³Department of Biomedical Engineering University of Minnesota, Minneapolis, MN, U.S.A

⁴Boston Scientific Neuromodulation, Valencia, CA, U.S.A

⁵Department of Biological Sciences and the Weldon School of Biomedical Engineering Purdue University, West Lafayette, IN, U.S.A

⁶Department of Biomedical Engineering University of Michigan, Ann Arbor, MI, U.S.A

Abstract

Advanced fabrication techniques have now made it possible to produce microelectrode arrays for recording the electrical activity of a large number of neurons in the intact brain for both clinical and basic science applications. However, the long-term recording performance desired for these applications is hindered by a number of factors that lead to device failure or a poor signal-to-noise ratio (SNR). The goal of this study was to identify factors that can affect recording quality using theoretical analysis of intracortical microelectrode recordings of single-unit activity. Extracellular microelectrode recordings were simulated with a detailed multi-compartment cable model of a pyramidal neuron coupled to a finite element volume conductor head model containing an implanted recording microelectrode. Recording noise sources were also incorporated into the overall modeling infrastructure. The analyses of this study would be very difficult to perform experimentally; however, our model-based approach enabled a systematic investigation of the effects of a large number of variables on recording quality. Our results demonstrate that recording amplitude and noise are relatively independent of microelectrode size, but instead are primarily affected by the selected recording bandwidth, impedance of the electrode-tissue interface, and the density and firing rates of neurons surrounding the recording electrode. This study provides the theoretical groundwork that allows for the design of the microelectrode and recording electronics such that the SNR is maximized. Such advances could help enable the long-term functionality required for chronic neural recording applications.

1. Introduction

Although chronic extracellular spike recordings have several clinical and basic science applications (Hochberg *et al.*, 2006; Kennedy and Bakay, 1998; Clement *et al.*, 1999), the ability to successfully record individual neurons over a long period of time is hindered by several factors. One of the main reasons for the poor chronic recording capabilities of microelectrode arrays is hardware or device failure (e.g. lead-wire fracture, degradation of the electrode insulation, loosening of the head implant) (Suner *et al.*, 2005; Hochberg *et al.*, 2006; Williams *et al.*, 1999; Vetter *et al.*, 2004). Another major reason for the poor long-

term performance of these cortical microelectrodes is a low recording signal-to-noise ratio (SNR). A low SNR can result from a variety of circumstances including the formation of a fibrous encapsulation layer stemming from a foreign body reaction around the electrode (Grill and Mortimer, 1994; Turner *et al.*, 1999; Szarowski *et al.*, 2003). This high impedance layer increases thermal noise levels (Johnson *et al.*, 2005; Ludwig *et al.*, 2006; Otto *et al.*, 2006) and effectively isolates the electrode from neurons in the surrounding gray matter (Turner *et al.*, 1999). The firing of several neurons in the surrounding biological media can also lead to the inability to preferentially record from a single cell (i.e. biological noise) (Ludwig *et al.*, 2006; Martinez *et al.*, 2009).

The goal of this study was to develop new techniques to investigate the variables that affect recording quality. Specifically, this study utilized a computational model to investigate the effects of microelectrode contact size and major noise sources on the quality of chronic intracortical microelectrode recordings of single-unit activity. This type of analysis would be extremely difficult to perform experimentally; therefore, we modified a previously-described computational model of cortical recording (Moffitt and McIntyre, 2005) to estimate recordings for a range of electrode designs resembling the planar microelectrodes fabricated at the University of Michigan and NeuroNexus Technologies (Ann Arbor, MI). Noise sources were also incorporated into the overall modeling infrastructure to estimate the thermal and biological noise levels experienced during chronic intracortical recordings.

The analysis performed in this study overcomes some of the limitations of previous theoretical studies by incorporating both a detailed neural source model and an explicit representation of the recording microelectrode to simulate extracellular recordings. Recording noise was also estimated with a thermal noise model parameterized with *in vitro* and *in vivo* impedance measurements along with a detailed biological noise model. The modeling infrastructure developed in this study provided a means to investigate a large number of variables relevant to single-unit recordings and represented the first study in which the effects of a detailed neural source, electrode geometry, noise models, and band-pass filtering were all incorporated into a single model. The model analysis showed that recording amplitude and noise are affected by the recording bandwidth, electrode impedance (determined by both the electrode size and tissue response near the electrode), and the density and firing rates of neurons surrounding the recording electrode. These type of variables need to be considered when analyzing chronic extracellular microelectrode recordings of single-unit activity. Preliminary portions of this work have been presented as a conference paper (Lempka *et al.*, 2006).

2. Methods

The goal of this study was to evaluate extracellular single-unit recording and recording noise for microelectrodes of different sizes. An overall recording signal-to-noise ratio (SNR) was calculated for each contact size by combining the model estimates for the peak-to-peak recording amplitude and the standard deviation of the recording noise (figure 1). The peak-to-peak recording amplitude was estimated using the coupled neuron model and finite-element model (FEM) described below. Recording noise was estimated by combining model predictions of thermal and biological noise sources.

2.1. Cortical recording model

The computational model of cortical recording used in this study included two major components: an electrical volume conductor and an electrical source model (figure 2) (Moffitt and McIntyre, 2005). The electrical volume conductor consisted of a FEM of a rat head with a silicon-substrate microelectrode inserted in the cortex (figure 2(A)). The electrical source model consisted of a multi-compartment cable model of a layer V

pyramidal neuron (figure 2(B)) (Mainen *et al.*, 1995; Mainen and Sejnowski, 1996; Moffitt and McIntyre, 2005).

2.1.1. Electrical volume conductor model—The volume conductor model contained four concentric spheres representing the brain, cerebrospinal fluid (CSF), skull, and scalp with radii of 8000, 8500, 9000, and 10,000 μm and electrical resistivities of 300, 56, 16,000, and 230 $\Omega\text{-cm}$, respectively (figure 2(A)). Magnetic resonance imaging (MRI) from previous experimental studies was used to determine the model parameters: head diameter and thickness of the skull and scalp layers (Ogiue-Ikeda *et al.*, 2003), electrical resistivities (Haueisen *et al.*, 2002), and CSF thickness (Franconi *et al.*, 2000; Thorsen *et al.*, 2003; Liu *et al.*, 2004). A 20 μm thick domain of higher resistivity (600 $\Omega\text{-cm}$) was incorporated around the electrode to account for the encapsulation layer that forms as a result of the foreign body reaction. The encapsulation layer thickness was similar to what has been observed experimentally (Szarowski *et al.*, 2003; Turner *et al.*, 1999) and the encapsulation resistivity was based on measurements performed in a peripheral nerve study (Grill and Mortimer, 1994). The FEM also included explicit representation of a silicon-substrate microelectrode. The electrode shank had a width of 107 μm , length of 2000 μm , and a thickness of 15 μm (figure 2(A)). The microelectrode contacts were circular with radii of 7.5, 11.5, 15, or 20 μm corresponding to approximate surface areas of 177, 413, 703, or 1250 μm^2 , respectively. These contact sizes are often used experimentally and are commercially available from NeuroNexus Technologies (Ann Arbor, MI) (Ward *et al.*, 2009; Otto *et al.*, 2006; Vetter *et al.*, 2004). The volume conductor models were assumed to be purely resistive (Logothetis *et al.*, 2007) and were generated in ANSYS v8.0 (Ansys, Inc., Canonsburg, PA). The models were discretized in space using tetrahedral elements (ANSYS element SOLID98) that consisted of 10 nodes, one node at each of the 4 vertices and bisector nodes on each of the 6 edges. The nodal density was non-uniform with a higher node density region-of-interest (ROI) consisting of the electrode and brain tissue in a $500 \times 500 \times 500 \mu\text{m}^3$ box surrounding the recording contact. The FEM consisted of over 660,000 nodes. Load and boundary conditions were necessary to achieve a model solution. The load condition consisted of a current source located at the electrode contact (reciprocal solution – rationale described below) and the boundary condition required the voltage attenuate to zero at the bottom of the head. The electrostatic model was solved in ANSYS with an iterative Jacobi conjugate gradient solver.

2.1.2. Electrical source model—The electrical source model used in this study was a multi-compartment cable model of layer V pyramidal cell from the cat visual cortex (figure 2(B)) (Mainen *et al.*, 1995; Mainen and Sejnowski, 1996). The model geometry was derived from a three-dimensional neuroanatomical reconstruction and the membrane biophysics were based on voltage-clamp and current-clamp measurements describing the behavior of the membrane ion channels. Modifications to the neuron model included removing the compartments of dendritic processes that intersected the recording electrode and by increasing the number of axonal compartments. An action potential was generated in the model by incorporating excitatory synaptic inputs in the apical dendrites (Moffitt and McIntyre, 2005). Simulations were performed in NEURON v5.8 to solve the transmembrane currents generated in each of the 531 compartments (Hines and Carnevale, 1997).

2.1.3. Model coupling—In the coupled FEM-neuron model, each compartment of the neuron model is represented as an independent current source (i.e. the time-dependent transmembrane currents computed in NEURON) at the appropriate spatial location in the FEM. The simulated recorded voltage waveform was then calculated by summing the voltages generated at the electrode contact by each of the transmembrane currents of the individual neural compartments. The fundamental task was to calculate the voltage

impressed at the electrode contact for a given current at an arbitrary point in the volume conductor. This can be formulated mathematically with the following expression:

$$\Phi = \mathbf{K}\mathbf{J} \quad (1)$$

where Φ is a $(1 \times t)$ vector containing the recorded voltage at t instances in time, $\mathbf{K}$ is a $(1 \times n)$ vector containing the voltages that would be impressed at the electrode contact for a unit current at the location of each of the n individual neuron compartments, and $\mathbf{J}$ is a $(n \times t)$ matrix containing the transmembrane currents for the individual neuron compartments at each time step. The $\mathbf{J}$ matrix was calculated in NEURON, while each value in the $\mathbf{K}$ vector was derived from the FEM using a reciprocal solution. Briefly, this reciprocal solution involved placing a unit current source (i.e. 1 A) at the electrode contact and solving for the scalar potentials generated at each node in the volume conductor mesh. By the theorem of reciprocity, the voltage at a given node in the mesh can be interpreted as the voltage that would be generated at the recording electrode for a unit current. Therefore, the contribution of each neural compartment to the recorded waveform (i.e. individual values in the $\mathbf{K}$ vector) could be calculated using interpolation of the voltages from the nearest nodes surrounding each neuronal compartment.

2.2. Noise models

2.2.1. Thermal noise model—One of the major noise sources encountered during microelectrode recordings is thermal noise, also called Johnson-Nyquist noise, generated by the random thermal motion of charge carriers in a resistive material. For cortical microelectrode recordings, the real (i.e. resistive) component of the system impedance is highly dependent on frequency; therefore, to develop an accurate model of thermal noise, impedance measurements must be taken over the recording bandwidth. To derive a parametric equation describing the microelectrode impedance as a function of frequency, *in vitro* and *in vivo* impedance spectroscopy measurements were used to parameterize a previously-published impedance model of chronically implanted cortical microelectrodes (figure 3(A)) (Johnson et al., 2005; Otto et al., 2006; Williams et al., 2007).

In this spatially-lumped impedance model, the electrode-electrolyte interface is represented by a constant phase element (CPE) with a magnitude scaling factor (K) and a phase factor (α) defined for $0 \leq \alpha \leq 1$.

$$Z_{\text{CPE}} = \frac{K}{(j\omega)^\alpha} \quad (2)$$

The CPE accounts for the pseudo-capacitive behavior of the electrode-electrolyte interface and is based on empirical data (McAdams *et al.*, 1995). The CPE is connected in series with an encapsulation resistance, R_{en} , which represents the electrode encapsulation formed as part of the foreign body reaction (figure 3(A)) (Grill and Mortimer, 1994). The resistance of the extracellular space is represented by R_{ex} and the cellular tissue component is represented by a parallel combination of a specific membrane conductance (g_m) and capacitance (c_m) that is multiplied by a membrane area scaling term (A_m) (figure 3(A)). The values of g_m and c_m are 0.3 mS/cm² and 1 μ F/cm², respectively (Buitengeweg *et al.*, 1998). The shunt capacitance of the electrode shank, represented by C_{sh} , was found to be < 10 pF and was assigned a value of 10 pF in the model analysis (Otto et al., 2006). The equation describing the impedance of the entire model was:

$$Z_{\text{model}} = \frac{1}{j\omega C_{\text{sh}} + \frac{1}{K(j\omega)^{-\alpha} + R_{\text{en}} + \frac{R_{\text{ex}}}{1 + A_m(j\omega \tau_m + \tau_m)}}} \quad (3)$$

Average model parameters for the electrode component of the impedance model (K and α) for each microelectrode contact size were determined by a nonlinear regression of *in vitro* electrode impedance spectroscopy (EIS) measurements. Average model parameters for the tissue component (R_{ex} , R_{en} , and A_m) of the impedance model described above were estimated from *in vivo* EIS measurements of microelectrode arrays chronically implanted in rats using a previously-described nonlinear regression algorithm (Otto *et al.*, 2006). The parameters R_{ex} , R_{en} , and A_m were assumed to be independent of electrode contact size. For each microelectrode contact size, the average parameter values for both the electrode and tissue components were combined and used to derive an expression for the recording impedance as a function of frequency according to (3). The model fit quality for the electrode and tissue parameters was assessed by calculating the coefficient of determination for both the real and imaginary components. If either value was less than 0.98, the individual recording site was not included in the pool of recording sites used to determine the average model parameters.

After determining the parameter values in (3), the thermal noise spectral density was estimated with the Johnson-Nyquist formula:

$$S_v(\omega) = 2kT \text{Re}\{Z(\omega)\} \quad (4)$$

where k represents the Boltzmann constant and T is the absolute temperature. The equation above is valid for any passive, reciprocal network and can be used to describe the noise voltage across two arbitrary terminals, such as the working and ground electrodes (Papoulis, 1984). The effects of bandpass filtering performed during single-unit microelectrode recordings were accounted for using the following equation:

$$S(\omega) = S_v(\omega) |H_{\text{sig}}(\omega)|^2 \quad (5)$$

where H_{sig} represents the transfer function of the combined filter stages. After estimating the noise spectral density, the noise variance was predicted by integration. Because the noise was zero-mean, integration of the autospectral density led directly to the noise variance.

The thermal noise spectrum, $S(\omega)$, was evaluated over the frequency range of 0–20 kHz at a frequency resolution of 1 Hz, corresponding to a sampling rate of 40 kHz and a signal length of one second for the discrete Fourier transform of the equivalent time-domain signal. Unless otherwise specified, H_{sig} consisted of a two-pole high-pass Butterworth filter with a cutoff frequency of 450 Hz and a two-pole low-pass Butterworth filter with a cutoff frequency of 5 kHz to simulate a typical recording bandwidth of 450–5000 Hz (Otto *et al.*, 2006; Vetter *et al.*, 2004). The temperature in (4) was set equal to a physiological temperature of 37°C. All of the numerical methods described above were performed using MATLAB 7.6 (MathWorks, Natick, MA).

2.2.2. Biological noise model—During intracortical microelectrode recordings, biological noise mainly arises from the activity of several hundred neurons in the tissue surrounding the recording microelectrode and represents a second major source of noise. In this study, biological noise was modeled by placing hundreds of neurons around the

recording microelectrode in the coupled FEM-neuron model (figure 4(B)). The 325 neurons were the same multi-compartment cable model described above, positioned around the recording contact with their somas located within an approximate $400 \times 400 \times 200 \mu\text{m}^3$ ROI. Neurons in the motor cortex are arranged in 100–300 μm wide columns (Meyer, 1987) and thus the ROI which contains neurons more than 200 μm from the recording electrode is representative of the dimensions that are seen physiologically. Experimental and theoretical studies have also shown that small voltage signals are detected for neurons farther than 100–150 μm from the recording electrode (Henze *et al.*, 2000; Moffitt and McIntyre, 2005; Csicsvari *et al.*, 2003). Therefore extending the dimensions of the ROI beyond 200 μm would likely not produce significant changes in the model results. This ROI was translated a distance of 50 μm normal to the electrode surface to simulate the region of decreased neural density near the recording electrode that results from the foreign-body response (Biran *et al.*, 2005). The 325 model neurons resulted in a neuronal density of 9.5×10^6 neurons/ cm^3 representative of the average neuronal density of 9.9×10^6 neurons/ cm^3 reported for the motor cortex (Cragg, 1967). Neurons were placed 17 μm apart in the x-z plane and the individual vertical locations in the y axis were randomly determined (figure 4(B)).

The individual neurons were simulated to generate a train of action potentials with random start times at a rate of 20 Hz by periodic excitatory synaptic inputs at the apical dendrites. The transmembrane currents for each compartment of the neuron model were solved in NEURON for a total simulation time of one second. The voltage signal recorded at the microelectrode contact was then calculated using the coupled FEM-neuron model described above for each of the 325 model neurons and the individual results superimposed to determine the overall “noisy” voltage recording. This recorded signal was then band-pass filtered over a typical recording bandwidth (i.e. 450–5000 Hz). Neural spikes in the recorded waveform were detected using a standard threshold detection method (Lewicki, 1998; Vetter *et al.*, 2004; Ludwig *et al.*, 2006). A threshold for action potential detection was set at three times the standard deviation of the entire voltage recording. Individual spikes were detected and a three millisecond window (1 ms before the spike and 2 ms after the spike) was used to classify the data falling within this window as an action potential and the remaining data was considered noise. The biological noise was calculated as the standard deviation of the remaining noise component of the voltage recording.

Ten different neuron distributions were generated to account for possible variability in the estimated biological noise levels due to the random placement of the model neurons surrounding the recording microelectrode. For each distribution, the biological noise was estimated for 10 separate voltage recordings (i.e. 10 different random firing times for the individual neurons) to account for possible variability in the biological noise levels due to the random firing times of the individual model neurons. This analysis was performed for each microelectrode contact size using the same neuron meshes and firing times.

2.2.3. Total recording noise—The total recording noise (σ_{noise}) for each microelectrode contact size was determined as the square root of the sum of the thermal noise and biological noise variances:

$$\sigma_{\text{noise}} = \sqrt{\sigma_t^2 + \sigma_b^2} \quad (6)$$

where σ_t and represent σ_b represent the standard deviations of the thermal and biological noise, respectively.

2.2.4. SNR analysis—The simulated neural recordings and noise were used to estimate the SNR for each contact size. The SNR for a given contact size was defined as the peak-to-

peak amplitude of the simulated neural recording divided by twice the standard deviation of the total recording noise (Nordhausen et al., 1996).

2.3 Effects of filter settings on recording quality

When filtering single-unit recordings, the selected cutoff frequencies can vary, but a typical pass band lies somewhere in the range of 100 – 10,000 Hz (Otto *et al.*, 2006; Vetter *et al.*, 2004; Hashimoto *et al.*, 2003; Suner *et al.*, 2005). To provide a more detailed investigation of the effects of band-pass filtering on recording quality, recording amplitude and noise were estimated for two conditions: 1. the high-pass cutoff frequency (f_{high}) was varied over a range of 10 – 1000 Hz with a fixed low-pass cutoff frequency (f_{low}) of 5 kHz, and 2. f_{high} was fixed at 450 Hz and f_{low} was varied from 1 – 10 kHz. The band-pass filter used in this analysis was a Butterworth filter with a 2-pole high-pass filter and a 2-pole low-pass filter.

2.4. Electrode impedance spectroscopy

EIS measurements were performed for both *in vitro* and *in vivo* conditions using an Autolab potentiostat (PGSTAT12, Eco Chemie, Utrecht, The Netherlands) with a built-in frequency response analyzer (Brinkmann Instruments, Westbury, NY). In both situations, a 25 mV (rms) sine wave was applied at a given frequency and the current output measured. The impedance at a specific frequency was calculated in the frequency domain using Ohm's law (i.e. $Z(f) = V(f) / I(f)$ where f is the specified frequency).

2.4.1. In vitro EIS—Cortical microprobes having contact sites of 177, 413, 703, and 1250 μm^2 were obtained from NeuroNexus Technologies and tested using a standard three-electrode cell configuration. In this three-electrode configuration, a cortical microelectrode contact served as the working electrode, the reference electrode was a saturated calomel electrode, and a stainless steel (316SS-grade) wire served as the auxiliary electrode. *In vitro* EIS measurements were performed at 37°C in a beaker filled with 500 mL of 0.1 M phosphate buffered saline (PBS) (pH=7.4). All *in vitro* measurements were performed inside a Faraday cage to help minimize noise that would contaminate the impedance measurements. EIS measurements were performed at 31 logarithmically-spaced frequencies ranging from 100 Hz to 10 kHz (10 frequency points/decade). These *in vitro* EIS measurements were used to estimate the electrode-electrolyte interface parameters (K and α) in the impedance model described in 2.2.1.

2.4.2. In vivo EIS—Previously-published *in vivo* EIS measurements were used to estimate the encapsulation, cellular, and extracellular components (R_{en} , A_{m} , and R_{ex}) of the impedance model described in 2.2.1 (Johnson et al., 2005; Otto et al., 2006). These *in vivo* EIS measurements were made on six silicon-substrate microelectrode arrays implanted in the motor cortex of four Sprague-Dawley rats (250–300 g, implanted for 19, 33, 94, and 97 days). The electrode arrays consisted of iridium contacts that were 703 μm^2 in size. Measurements were performed using a two-electrode cell configuration in which the working electrode was an individual microelectrode contact and the counter electrode was a stainless steel (316SS-grade) bone screw. Measurements were performed at 11 frequencies ranging from 100 Hz to 10 kHz. A typical impedance spectra measured *in vivo* is shown in figure 3(B). Surgical procedures for these implants have been previously described (Otto et al., 2006).

3. Results

3.1. Signal amplitude estimation

Recording amplitude for each microelectrode recording contact size considered in this study was estimated with the coupled FEM-neuron model. In this analysis, a model neuron was

placed with its soma located 50 μm normal to the center of the recording site. The simulated extracellular recordings were also filtered over a typical recording bandwidth (i.e. 450–5000 Hz). Model analysis produced peak-to-peak signal amplitudes of 205, 199, 194, and 186 μV for contact surface areas of 177, 413, 703, and 1250 μm^2 , respectively (figure 5(D)).

3.2. Noise estimation and SNR analysis

3.2.1. Impedance parameter estimation—*In vitro* EIS measurements were performed to determine the electrode parameters, K and α . Multiple microelectrode arrays were tested for each contact size ($n = 28, 44, 45$, and 47 contacts for contact sizes 177, 413, 703, and 1250 μm^2 , respectively). EIS measurements were performed in triplicate and averaged to help reduce variability inherent to the measuring system. The electrode parameters for each individual recording site were determined using nonlinear weighted least squares. The average values for K were 2.29 ± 0.33 , 1.22 ± 0.23 , 0.97 ± 0.21 , and $0.77 \pm 0.21 \text{ G}\Omega\text{s}^{-\alpha}$ and α were 0.88 ± 0.01 , 0.88 ± 0.01 , 0.89 ± 0.02 , and 0.89 ± 0.03 for electrode sizes of 177, 413, 703, and 1250 μm^2 , respectively.

The tissue parameters of the impedance model (R_{en} , R_{ex} , and A_{m}) were determined from *in vivo* EIS measurements. Data was obtained from six separate microelectrode arrays implanted in the motor cortex of four different rats ($n = 73$ recording sites). The parameter values were estimated using a previously-published nonlinear regression algorithm (Otto *et al.*, 2006). The average tissue parameter values $298 \pm 96 \text{ k}\Omega$, $768 \pm 593 \text{ k}\Omega$, and $1.68 \pm 1.27 \times 10^{-4} \text{ cm}^2$ for R_{en} , R_{ex} , and A_{m} respectively.

3.2.2. Thermal noise—The thermal noise for each microelectrode size was determined by combining the average tissue component parameters (R_{en} , R_{ex} , and A_{m}) with the average electrode parameters (K and α) to estimate the model impedance as function of frequency according to (3). The thermal noise spectral density was estimated from the impedance spectrum with (4) and the effects of band-pass filtering were accounted for with (5). Because the noise was zero-mean, integration of the noise spectral density led directly to the noise variance. The parameters shown in figure 3(D) resulted in thermal noise levels with standard deviation of 6.32, 6.23, 6.20, and 6.18 μV for electrode sizes of 177, 413, 703, and 1250 μm^2 , respectively (figure 5(E)). These values show the expected result of decreasing thermal noise with increasing electrode surface area; however, the differences between the individual electrode sizes were small. The average thermal noise level (independent of contact size) was 6.23 μV .

While the results above provided an estimate of the thermal noise that may be encountered experimentally ($\sim 6 \mu\text{V}$), thermal noise levels will be highly dependent on the impedance of the electrode-tissue interface for each individual recording site (due to the foreign body reaction) and the selected recording bandwidth (i.e. a wider recording bandwidth will increase thermal noise levels). To address some of the possible variability in thermal noise, we considered multiple impedance conditions and recording bandwidths. The recording bandwidth in the analysis described above was a standard recording bandwidth for silicon-substrate microelectrodes (i.e. 450–5000 Hz); however, experimentalists frequently use wider pass bands in microelectrode recordings (Hashimoto *et al.*, 2003; Suner *et al.*, 2005; Drake *et al.*, 1988). To look at the effect of a wide pass band on thermal noise, we performed the same model analysis described above with a pass band of 0.1 – 10 kHz. The wide pass-band resulted in an average 35% increase in thermal noise along with a 25% increase in the action potential amplitudes recorded at the microelectrode. Only small differences were observed between the individual contact sizes and the specific changes for an electrode size of 703 μm^2 are shown in table 1.

Another factor that can significantly affect the recording thermal noise is the large variability in the tissue response around individual recording sites that has been shown with both histological techniques and impedance measurements (Williams *et al.*, 2007). Variability in the tissue response produces differences in the electrode-tissue interface impedance between various contacts that can lead to corresponding differences in thermal noise. Therefore, we also investigated the effects of variable impedance conditions at the electrode-tissue interface. A low electrode-tissue interface impedance (i.e. low degree of tissue response) resulted in a large decrease in the thermal noise levels relative to the average tissue parameter values (37–45%). A high electrode-tissue interface impedance (i.e. high degree of tissue response) only produced a small increase (5–6%) in thermal noise levels relative to the average parameter values determined from the *in vivo* EIS measurements (table 1). Table 1 describes the tissue parameter values for the low and high electrode-tissue interface impedance conditions and the specific differences in thermal noise levels for a contact size of 703 μm^2 . Tissue parameters were $R_{\text{en}} = 10 \text{ k}\Omega$, $R_{\text{ex}} = 100 \text{ k}\Omega$, and $A_{\text{m}} = 1 \times 10^{-5} \text{ cm}^2$ for the low impedance condition (Z_{low}) and $R_{\text{en}} = 500 \text{ k}\Omega$, $R_{\text{ex}} = 2 \text{ M}\Omega$, and $A_{\text{m}} = 1 \times 10^{-3} \text{ cm}^2$ for the high impedance condition (Z_{high}). The tissue parameters were determined from the range of values produced in the model fitting of the *in vivo* EIS data described in 2.2.1 and 2.3.2. The electrode parameters (K and α) for all three impedance conditions and the tissue parameters for the average impedance condition (Z_{avg}) were the average model parameters described in 3.2.1.

3.2.3. Biological noise—Biological noise levels were calculated as described in 2.2.2. Biological noise levels of 10.3 ± 0.4 , 10.3 ± 0.4 , 10.2 ± 0.4 , and $9.9 \pm 0.4 \text{ }\mu\text{V}$ were estimated for contact surface areas of 177, 413, 703, and 1250 μm^2 , respectively (figure 5(E)). The biological noise decreased for large contact sizes; however, the differences between the individual contact sizes were small. The average biological noise in the simulated extracellular recordings (independent of contact size) was 10.2 μV .

Due to the complex anatomical organization and electrical behavior of neurons in the neocortex, it is likely that the biological noise levels encountered during intracortical microelectrode recordings can also be highly variable. Therefore, we investigated the biological noise expected for different neuronal densities and firing rates. We compared the biological noise estimated for a neuronal density similar to the average neuronal density reported by Cragg (1967) for the motor cortex (i.e. $9.5 \times 10^6 \text{ neurons/cm}^3$) to a low cell density (i.e. $2.4 \times 10^6 \text{ neurons/cm}^3$). The low neuronal density produced much lower biological noise at the recording microelectrode (62% decrease, table 1). No major differences were observed between the individual contact sizes and table 1 shows the specific biological noise values for a contact size of 703 μm^2 .

Another factor that will likely produce large differences in the observed biological noise is the complex electrical behavior of neurons in the cortex. In the analysis described above, biological noise was simulated with neurons firing at a rate of 20 Hz which is a frequency of single-unit activity that can be observed in the motor cortex, especially during movement (Evarts, 1964; Fetz, 1969; Zhang *et al.*, 1997). However, a large number of neurons often remain quiescent or have a lower firing rate (Goldberg *et al.*, 2002). In order to simulate decreased neuronal activity, biological noise levels were also estimated for neurons firing at 5 Hz. This decrease in overall neural activity produced a dramatic decrease in the biological noise levels (60–61% decrease, table 1). No major differences were observed between the individual contact sizes.

The selected recording bandwidth also had a dramatic effect on the biological noise levels. A wide recording bandwidth (i.e. 0.1–10 kHz) produced a large increase in the biological

noise (74–75% increase, table 1). Only small differences were observed between the individual contact sizes.

3.2.4. Total recording noise and SNR analysis—The total recording noise was calculated for each recording contact size according to (6) and was estimated as 12.1, 12.0, 11.9, and 11.7 μV for electrode surface areas of 177, 413, 703, and 1250 μm^2 , respectively (figure 5(E)). The recording SNR for each contact size was then calculated as the peak-to-peak recording amplitude divided by twice the standard deviation of the recording noise: 8.5, 8.3, 8.1, and 8.0 for contact surface areas of 177, 413, 703, and 1250 μm^2 , respectively (figure 5(F)).

3.3. Effects of filter settings on recording quality

As can be seen in figure 6(E), band-pass filtering produced significant distortions in the shape of the recorded action potential waveform. The selected f_{high} led to the largest degree of distortion in the action potential waveform. f_{high} produced the large negative rebound in the slow repolarization phase similar to what has been previously shown in the literature (Quiñero, 2009; Nelson *et al.*, 2008; Wiltchko *et al.*, 2008), along with phase shifts in the peak of the repolarization phase. f_{high} also produced the largest degree of attenuation in the peak of the action potential during the depolarization phase (Wiltchko *et al.*, 2008). In figure 6(I), it is clear that increasing f_{high} leads to significant distortion of the recorded action potential waveform and a decrease in the peak-to-peak recording amplitude. Increasing f_{high} also produces a dramatic decrease in the biological noise along with a small decrease in the thermal noise. Figure 6(II) shows that f_{low} has a much smaller effect on waveform distortion relative to f_{high} . It is also clear that the peak-to-peak recording amplitude and biological noise begin to level off as f_{low} is increased to the 3–5 kHz range; however, the thermal noise continually increases (figure 6(B)–(C)). This leads to a maximal SNR when f_{low} is in the 3–5 kHz range and corresponds to the range typically selected in experimental applications (figure 6(D)).

4. Discussion

The goal of this study was to quantitatively determine the effect of different variables on the recording quality of single-unit activity. This study utilized theoretical techniques to perform a systematic analysis that would be extremely difficult to perform experimentally. Model analysis produced results that resembled experimental measurements and illustrated a number of factors that need to be considered when attempting to optimize recording quality.

4.1. Recording amplitude

For the recording site surface areas examined in this study (i.e. 177 – 1250 μm^2), the coupled FEM-neuron model estimated minor differences in the recording amplitude that were ~10% of the total recording amplitude. A wider range of contact sizes has been examined in a previous modeling study and a large decrease in the recording amplitude was observed for extremely large contacts (e.g. 10,000 μm^2) (Moffitt and McIntyre, 2005). However, we focused on standard contact sizes that are used experimentally, and to perform the EIS measurements for the thermal noise analysis, we needed to use commercially available microelectrodes for testing (see 2.2.1 and 2.3). Therefore, we were unable to thoroughly address the effect of large contacts.

4.2. Noise levels

There are several possible sources of noise that can be encountered during microelectrode recordings of neural activity. Examples of these noise sources include thermal noise, electrical activity of neurons near the recording electrode (i.e. biological noise), 1/f noise,

and capacitive coupling to power lines and lights (Thorp and Steinmetz, 2009; Najafi, 1994; Harrison, 2008). The model analysis performed in this study accounted for what are considered to be two of the main noise sources encountered in intracortical microelectrode recordings (i.e. thermal and biological noise) (Du *et al.*, 2009; Najafi, 1994).

4.2.1. Thermal noise—Thermal noise estimates exhibited minor differences between the recording contact sizes examined in this study (~2 %). For chronically implanted microelectrodes, the electrode-electrolyte interface impedance dominates the overall electrode-tissue interface impedance at low frequencies. Therefore, the major impedance differences between the individual contact sizes occurred in the low frequency range (i.e. < 1 kHz). Because these extracellular recordings were band-pass filtered (e.g. 450–5000 Hz), the low frequency information was attenuated and the impedance differences only resulted in small changes in thermal noise. A majority of the recording bandwidth consists of higher frequencies (i.e. > 1 kHz) to capture the large amount of high frequency information in extracellular action potential waveforms. As such, the thermal noise levels were dominated by the impedance in the higher frequency range (i.e. the tissue impedance).

While the theoretical analysis performed in this study provided an estimate of the thermal noise that may be encountered experimentally (~6 μV), thermal noise levels will be highly dependent on the impedance of the electrode-tissue interface for each individual recording site (due to the foreign body reaction) and the selected recording bandwidth (i.e. a wider recording bandwidth will increase thermal noise levels). To address some of the possible variability in thermal noise, we considered multiple impedance conditions and recording bandwidths. A wide recording bandwidth (100–10,000 Hz) resulted in a large increase in thermal noise levels (35%) and action potential amplitudes (25%) relative to a more standard recording bandwidth (i.e. 450–5000 Hz, table 1). A low electrode-tissue interface impedance (i.e. low degree of tissue response) showed a large decrease in the thermal noise levels (37–45%) with the largest decrease in thermal noise observed for the largest recording site (i.e. 1250 μm^2). This results suggests the electrode-electrolyte interface impedance contributes more significantly to the thermal noise when there is a low tissue impedance.

4.2.2. Biological noise—Biological noise models have been previously reported in the literature (Martinez *et al.*, 2009; Eaton and Henriquez, 2005); however, this study represented an advancement by incorporating both detailed neural source models and an explicit representation of the recording microelectrode into the model. The biological noise levels predicted in this study showed a slight decrease in the biological noise for large recording contacts (4 % decrease for a recording site of 1250 μm^2 relative to 177 μm^2). This trend was opposite to the common view in the field of neural recording where it is typically believed that large surface area recording sites result in more neural “hash” because large recording sites are presumably more sensitive to neural currents from a larger area of tissue and therefore a larger number of neurons. However, the decrease in biological noise for large recording sites was most likely related to the lower electrode impedance that produces a lower voltage at the recording contact for a given amount of current (Moffitt and McIntyre, 2005). Low electrode impedance was the same reason large contacts produced lower recording amplitudes (186 μV for an electrode surface area of 1250 μm^2 relative to 205 μV for an electrode surface area of 177 μm^2).

Due to the complex anatomical organization and electrical behavior of neurons in the neocortex, it is likely that the biological noise levels encountered during intracortical microelectrode recordings can be highly variable. Therefore, we investigated the biological noise expected for different neuronal densities and firing rates. Because the cortex is organized in cell-dense columns separated by cell-sparse regions (neuronal density also varies between cortical areas and individual cortical layers), the neuron density surrounding

the recording microelectrode is highly dependent on the position of the recording contact. A low neuronal density produced much lower biological noise at the recording microelectrode (62% decrease, table 1). Another factor that will likely produce large differences in the observed biological noise is the complex electrical behavior of neurons in the cortex. A decrease in overall neural activity (from 20 Hz to 5 Hz) produced a dramatic decrease in the biological noise levels (60–61% decrease, table 1). According to these modeling results, changes in the firing rates and firing patterns of neurons near the recording microelectrode will lead to non-stationarity in the recording noise, which has been observed experimentally (Fee *et al.*, 1996).

The selected recording bandwidth also had a dramatic effect on the biological noise levels. A wide recording bandwidth (i.e. 0.1–10 kHz) produced a large increase in the biological noise (74–75% increase, table 1). This increase in biological noise was almost entirely attributed to the 100 Hz high-pass cutoff frequency that produced increased signal energy in the low frequency range of the recorded signal (figure 6(C)).

4.3. Comparison to Experimental Results

The average peak-to-peak recording amplitude, noise levels, and resulting SNR are similar to the experimental values observed in chronic recordings with silicon-substrate microelectrodes (Vetter *et al.*, 2004; Otto *et al.*, 2006; Ludwig *et al.*, 2006; Ward *et al.*, 2009; Suner *et al.*, 2005; Williams *et al.*, 1999). For a contact size of 703 μm^2 , the recording amplitude, noise, and SNR were 194 μV , 11.9 μV , and 8.1, respectively. For the same electrode size *in vivo*, Otto *et al.* (2006) and Ludwig *et al.*, (2006) reported average noise levels of 12.1 and 13.1 μV respectively. Ludwig *et al.*, (2006) also reported an average signal recording amplitude of 113 ± 13 μV that corresponded to an average SNR of 4.3 ± 1.0 . The recording amplitudes (186–205 μV) and the corresponding SNR's (8.0–8.5) estimated in our study were higher than the average values that are typically seen experimentally. The recording amplitude and SNR were estimated for a neuron located 50 μm from the recording site and represented a high recording quality within the range that can be seen experimentally (Vetter *et al.*, 2004). Single-unit recording amplitude can vary significantly depending on a number of factors (e.g. neuron geometry, position of the neuron relative to the recording site) and has been shown to vary between 50–800 μV for the type of microelectrode design considered in this study (Vetter *et al.*, 2004). The similarities in recording amplitude and noise between the model estimates and experimental values suggest the model detail was sufficient to capture a number of factors that contribute to intracortical microelectrode recording quality.

For the range of contact sizes examined in this study, the results showed that microelectrode size did not play a significant role in determining the recording quality. Increasing the contact surface area by seven times (177 μm^2 to 1250 μm^2), resulted in only a six percent decrease in SNR (8.5 to 8.0) (figure 5(F)). This trend has also been observed experimentally for a wide range of contact sizes during acute recordings with conical microelectrodes (Nordhausen *et al.*, 1994). Therefore, while electrode contact size is not the important feature when optimizing microelectrode design to improve recording quality, other issues such as the electrode-tissue interface impedance and recording bandwidth need to be considered. This finding supports current efforts to modify the electrode interface with novel materials such as applied polymers or drug-eluting coatings to reduce electrode impedance or minimize the foreign body reaction (Kim and Martin, 2006; Ludwig *et al.*, 2006). The relative independence of recording quality and microelectrode size should also allow investigators more freedom to design electrode geometries specific to the local neural anatomy in question. In addition, because the results of this study examining a planar electrode are similar to the experimental results for the conical electrode characterized by

Nordhausen et al., (1994), the results of this study can likely be generalized to multiple microelectrode geometries.

4.4. Effects of filter settings on recording quality

During neural recordings, the raw data is band-pass filtered to identify action potentials and to avoid confounding issues such as voltage drift, aliasing, excessive noise, etc. (Quian Quiroga, 2009). The use of causal filters during on-line analysis of neural recordings not only affects the estimated noise levels but also produces distortions in both the relative shape and amplitude of the action potential waveform. These filter-induced distortions result from the non-flat pass-band and a non-linear phase response of the band-pass filter and can make it more difficult to discriminate between action potentials generated from independent neurons (Wiltschko *et al.*, 2008). To provide a more detailed investigation of the effects of band-pass filtering on recording quality, recording amplitude and noise were estimated for two conditions: 1. a variable high-pass cutoff frequency (f_{high}) with a fixed low-pass cutoff frequency (f_{low}), and 2. a fixed f_{high} with a variable f_{low} . These conditions allowed us to isolate the effects of f_{high} and f_{low} on both recording amplitude and noise. The modeling approach used in this study also allowed us to independently analyze the effects of filter settings on thermal and biological noise sources. From these results, it is clear that band-pass filtering produces distortions in the shape of the recorded action potential waveform (figure 6(E)), decreases the peak-to-peak recording amplitude (figure 6(B)), and affects the composition and magnitude of the recording noise (figure 6(C)). Although causal filters are typically used when analyzing spike recording data, it is possible to minimize some of the distortions described above using off-line analysis with non-causal filters (Quian Quiroga, 2009; Wiltschko *et al.*, 2008).

4.5. Study limitations

4.5.1. Coupled FEM-neuron model—The recording model developed in this study utilized a simplified volume conductor model of a rat head coupled to an electrical source model of a layer V pyramidal cell from the cat visual cortex. The head model was generated with dimensions typical of a rat because the thermal noise model was developed with *in vivo* data measured in rats. A rat head model also allowed us to directly compare our results to the large amount of experimental data available in the literature (see 4.3). However, it is important to note that because the recording volume of a microelectrode is quite small (Moffitt and McIntyre, 2005), extending the dimensions of the head model would likely not affect the overall model results. Also, while the geometry of the electrical source model was based on a three-dimensional reconstruction of a pyramidal cell from the cat visual cortex, this neuron had the standard pyramidal cell geometry (i.e. complex apical and basal dendritic structures). This neuron model also utilized standard ion channel kinetics and densities based on experimental studies performed in several species (Mainen et al., 1995; Mainen and Sejnowski, 1996). For these reasons, the results presented in this study can be generalized to microelectrode recordings performed in multiple cortical areas and species.

The complex tissue encapsulation and bulk medium that surrounds chronically-implanted cortical microelectrodes creates a highly tortuous electrical environment that can affect the signals recorded from cortical neurons. Our recording model accounted for this complex environment with simplistic domains of uniform conductivities. This limitation may be particularly important in the context of the model encapsulation domain because of the lower conductivity and close proximity to the electrode. Incorporation of a more detailed encapsulation layer could affect the estimated signal and noise amplitudes, yet we expect the trends would be similar to those reported in this study. The volume conductor model was also assumed to be purely resistive and therefore underestimated the tissue impedance. A more complete model of the tissue impedance consists of both resistive and capacitive

components (McAdams and Jossinet, 1995; Bedard et al., 2004), although experimental impedance measurements have shown the impedance of cortical gray matter is relatively frequency-independent and can be accurately represented as a purely resistive volume conductor (Logothetis et al., 2007).

4.5.2. Thermal noise model—A possible limitation in the thermal noise model was the use of an equivalent circuit model containing spatially-lumped elements to describe recording in a spatially-distributed three-dimensional environment. Nonetheless, this model accurately describes measured impedance values (Otto et al., 2006; Williams et al., 2007) and allows straight forward characterization of the electrode and tissue components of the measured impedance. A second limitation in the thermal noise model was the use of *in vivo* EIS data from recording sites of only one size (i.e. $703 \mu\text{m}^2$) to determine the average tissue parameters of the impedance model. It is possible that the tissue parameters (R_{en} , R_{ex} , and A_{m}) could vary as a function of electrode size and might affect the thermal noise levels estimated for each contact size. On the other hand, differences in tissue parameters as a function of electrode size would likely be much smaller than the parameter variability attributed to the large variations in tissue response observed between individual recording sites *in vivo* (see the standard deviations of the average tissue parameters described in 3.2.1). Because of this large variability in the tissue response, it is difficult to assign a standard or definitive set of average impedance parameters. It is much more reasonable to investigate a range of impedance conditions that might be encountered experimentally, as performed in the analysis detailed in table 1. It is also important to recognize that the thermal noise model in this study only accounted for the thermal noise of the electrode and not the thermal noise encountered at the preamplifier. However, over a biological recording bandwidth (e.g. 450–5000 Hz), the electrode thermal noise dominates the characteristics of the electrode-preamplifier system (Najafi, 1994).

4.5.3. Biological noise model—Although the neural density of the biological noise model mimics the average neural density experimentally measured in the motor cortex, the density of the cortical layers is highly variable due to the detailed functional organization of the cortex. The cortical layers are somatotopically organized in cell-dense columns that are separated by cell-sparse regions (Meyer, 1987). The cell numbers, cell types, and cell sizes can also vary widely between the various cortical layers (Sloper et al., 1979; Meyer, 1987) along with the firing rates and patterns of cortical neurons (Goldberg *et al.*, 2002; Fetz, 1969; Evarts, 1964; Grammont and Riehle, 2003; Riehle *et al.*, 1997). Therefore, the biological noise encountered during intracortical microelectrode recordings will be highly dependent on the location of the electrode sites relative to the organization of the local cortical area. Another factor that can lead to variability in the biological noise is the degree of correlation between the firing of neurons within individual columns. In the biological noise model described in this study, we assumed zero correlation between individual neurons (i.e. individual neurons were assigned random firing times). Within motor columns it is likely that the individual neurons show nonzero correlation and the degree of correlation will vary during states of movement and rest (Riehle *et al.*, 1997; Grammont and Riehle, 2003). This complex cortical organization and neural behavior is the reason we estimated the biological noise under multiple conditions (i.e. cell densities and firing rates) (table 1). A major advantage of this model was the ability to investigate the biological noise for the described conditions and provide a range of biological noise that can be encountered experimentally.

5. Conclusion

This study utilized detailed computer models of cortical recording with silicon-substrate microelectrodes and experimental measurements of electrode impedance to investigate the

effects of electrode size and thermal and biological noise on recording quality. This type of analysis would be very difficult to perform experimentally; however, the model was able to generate recording amplitudes, noise, and SNR that resembled experimental values reported in the literature. Model analysis showed the smallest electrode size (i.e. $177 \mu\text{m}^2$) resulted in the highest SNR by providing increased signal recording amplitude with only a small increase in recording noise. However, this improvement was small (~6% relative to an electrode size of $1250 \mu\text{m}^2$) and recording quality was relatively independent of microelectrode size. Model analysis also showed theoretical levels of thermal and biological noise that can be expected in chronic intracortical microelectrode recordings and potential confounding factors (e.g. signal filtering, variable electrode-tissue interface impedance, neuron density and firing rates) that can significantly alter recording quality. The variables examined in this study need to be considered when analyzing cortical recording data and when optimizing the design of recording systems to maximize the long-term SNR desired for clinical and experimental applications.

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References

- Bedard C, Kroger H, Destexhe A. Modeling extracellular field potentials and the frequency-filtering properties of extracellular space. *Biophysical journal*. 2004; 86:1829–42. [PubMed: 14990509]
- Biran R, Martin DC, Tresco PA. Neuronal cell loss accompanies the brain tissue response to chronically implanted silicon microelectrode arrays. *Exp Neurol*. 2005; 195:115–26. [PubMed: 16045910]
- Buitenweg JR, Rutten WLC, Willems WPA, van Nieuwkastele JW. Measurement of sealing resistance of cell-electrode interfaces in neuronal cultures using impedance spectroscopy. *Medical & Biological Engineering & Computing*. 1998; 36:630–7. [PubMed: 10367450]
- Clement RS, Witte RS, Rousche PJ, Kipke DR. Functional connectivity in auditory cortex using chronic, multichannel unit recordings. *Neurocomputing*. 1999; 26-7:347–54.
- Cragg BG. The density of synapses and neurones in the motor and visual areas of the cerebral cortex. *J Anat*. 1967; 101:639–54. [PubMed: 4964696]
- Csicsvari J, Henze DA, Jamieson B, Harris KD, Sirota A, Bartho P, Wise KD, Buzsaki G. Massively parallel recording of unit and local field potentials with silicon-based electrodes. *Journal of neurophysiology*. 2003; 90:1314–23. [PubMed: 12904510]
- Drake KL, Wise KD, Farraye J, Anderson DJ, Bement SL. Performance of Planar Multisite Microprobes in Recording Extracellular Single-Unit Intracortical Activity. *Ieee Transactions on Biomedical Engineering*. 1988; 35:719–32. [PubMed: 3169824]
- Du J, Riedel-Kruse IH, Nawroth JC, Roukes ML, Laurent G, Masmanidis SC. High-resolution three-dimensional extracellular recording of neuronal activity with microfabricated electrode arrays. *Journal of neurophysiology*. 2009; 101:1671–8. [PubMed: 19091921]
- Eaton KP, Henriquez CS. Confounded spikes generated by synchrony within neural tissue models. *Neurocomputing*. 2005; 65:851–7.
- Evarts EV. Temporal Patterns of Discharge of Pyramidal Tract Neurons During Sleep and Waking in the Monkey. *Journal of neurophysiology*. 1964; 27:152–71. [PubMed: 14129768]
- Fee MS, Mitra PP, Kleinfeld D. Variability of extracellular spike waveforms of cortical neurons. *Journal of neurophysiology*. 1996; 76:3823–33. [PubMed: 8985880]
- Fetz EE. Operant conditioning of cortical unit activity. *Science*. 1969; 163:955–8. [PubMed: 4974291]

- Franconi F, Lemaire L, Marescaux L, Jallet P, Le Jeune JJ. In vivo quantitative microimaging of rat spinal cord at 7T. *Magnetic Resonance in Medicine*. 2000; 44:893–8. [PubMed: 11108626]
- Goldberg JA, Boraud T, Maraton S, Haber SN, Vaadia E, Bergman H. Enhanced synchrony among primary motor cortex neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of Parkinson's disease. *J Neurosci*. 2002; 22:4639–53. [PubMed: 12040070]
- Grammont F, Riehle A. Spike synchronization and firing rate in a population of motor cortical neurons in relation to movement direction and reaction time. *Biol Cybern*. 2003; 88:360–73. [PubMed: 12750898]
- Grill WM, Mortimer JT. Electrical-Properties of Implant Encapsulation Tissue. *Annals of Biomedical Engineering*. 1994; 22:23–33. [PubMed: 8060024]
- Harrison RR. The design of integrated circuits to observe brain activity. *Proceedings of the Ieee*. 2008; 96:1203–16.
- Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J Neurosci*. 2003; 23:1916–23. [PubMed: 12629196]
- Hauelsen J, Tuch DS, Ramon C, Schimpf PH, Wedeen VJ, George JS, Belliveau JW. The influence of brain tissue anisotropy on human EEG and MEG. *Neuroimage*. 2002; 15:159–66. [PubMed: 11771984]
- Henze DA, Borhegyi Z, Csicsvari J, Mamiya A, Harris KD, Buzsaki G. Intracellular features predicted by extracellular recordings in the hippocampus in vivo. *Journal of neurophysiology*. 2000; 84:390–400. [PubMed: 10899213]
- Hines ML, Carnevale NT. The NEURON simulation environment. *Neural Comput*. 1997; 9:1179–209. [PubMed: 9248061]
- Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M, Caplan AH, Branner A, Chen D, Penn RD, Donoghue JP. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature*. 2006; 442:164–71. [PubMed: 16838014]
- Johnson MD, Otto KJ, Kipke DR. Repeated voltage biasing improves unit recordings by reducing resistive tissue impedances. *Ieee Transactions on Neural Systems and Rehabilitation Engineering*. 2005; 13:160–5. [PubMed: 16003894]
- Kennedy PR, Bakay RA. Restoration of neural output from a paralyzed patient by a direct brain connection. *Neuroreport*. 1998; 9:1707–11. [PubMed: 9665587]
- Kim DH, Martin DC. Sustained release of dexamethasone from hydrophilic matrices using PLGA nanoparticles for neural drug delivery. *Biomaterials*. 2006; 27:3031–7. [PubMed: 16443270]
- Lempka SF, Johnson MD, Barnett DW, Moffitt MA, Otto KJ, Kipke DR, McIntyre CC. Optimization of microelectrode design for cortical recording based on thermal noise considerations. *Conf Proc IEEE Eng Med Biol Soc*. 2006; 1:3361–4. [PubMed: 17947023]
- Lewicki MS. A review of methods for spike sorting: the detection and classification of neural action potentials. *Network*. 1998; 9:R53–78. [PubMed: 10221571]
- Liu CH, D'Arceuil HE, de Crespigny AJ. Direct CSF injection of MnCl₂ for dynamic manganese-enhanced MRI. *Magnetic Resonance in Medicine*. 2004; 51:978–87. [PubMed: 15122680]
- Logothetis NK, Kayser C, Oeltermann A. In vivo measurement of cortical impedance spectrum in monkeys: implications for signal propagation. *Neuron*. 2007; 55:809–23. [PubMed: 17785187]
- Ludwig KA, Uram JD, Yang J, Martin DC, Kipke DR. Chronic neural recordings using silicon microelectrode arrays electrochemically deposited with a poly(3,4-ethylenedioxythiophene) (PEDOT) film. *J Neural Eng*. 2006; 3:59–70. [PubMed: 16510943]
- Mainen ZF, Joerges J, Huguenard JR, Sejnowski TJ. A model of spike initiation in neocortical pyramidal neurons. *Neuron*. 1995; 15:1427–39. [PubMed: 8845165]
- Mainen ZF, Sejnowski TJ. Influence of dendritic structure on firing pattern in model neocortical neurons. *Nature*. 1996; 382:363–6. [PubMed: 8684467]
- Martinez J, Pedreira C, Ison MJ, Quiroga R. Realistic simulation of extracellular recordings. *J Neurosci Methods*. 2009; 184:285–93. [PubMed: 19703490]
- McAdams ET, Jossinet J. Tissue Impedance - a Historical Overview. *Physiological Measurement*. 1995; 16:A1–A13. [PubMed: 8528108]

- McAdams ET, Lacknermeier A, McLaughlin JA, Macken D, Jossinet J. The Linear and Nonlinear Electrical-Properties of the Electrode-Electrolyte Interface. *Biosensors & Bioelectronics*. 1995; 10:67–74.
- Meyer G. Forms and spatial arrangement of neurons in the primary motor cortex of man. *J Comp Neurol*. 1987; 262:402–28. [PubMed: 3655019]
- Moffitt MA, McIntyre CC. Model-based analysis of cortical recording with silicon microelectrodes. *Clin Neurophysiol*. 2005; 116:2240–50. [PubMed: 16055377]
- Najafi K. Solid-State Microsensors for Cortical Nerve Recordings. *Ieee Engineering in Medicine and Biology Magazine*. 1994; 13:375–87.
- Nelson MJ, Pouget P, Nilsen EA, Patten CD, Schall JD. Review of signal distortion through metal microelectrode recording circuits and filters. *J Neurosci Methods*. 2008; 169:141–57. [PubMed: 18242715]
- Nordhausen CT, Maynard EM, Normann RA. Single unit recording capabilities of a 100 microelectrode array. *Brain Res*. 1996; 726:129–40. [PubMed: 8836553]
- Nordhausen CT, Rousche PJ, Normann RA. Optimizing recording capabilities of the Utah Intracortical Electrode Array. *Brain Res*. 1994; 637:27–36. [PubMed: 8180807]
- Ogiue-Ikeda M, Kawato S, Ueno S. The effect of repetitive transcranial magnetic stimulation on long-term potentiation in rat hippocampus depends on stimulus intensity. *Brain Research*. 2003; 993:222–6. [PubMed: 14642850]
- Otto KJ, Johnson MD, Kipke DR. Voltage pulses change neural interface properties and improve unit recordings with chronically implanted microelectrodes. *IEEE transactions on bio-medical engineering*. 2006; 53:333–40. [PubMed: 16485763]
- Papoulis, A. *Probability, Random Variables, and Stochastic Processes*. New York: McGraw-Hill; 1984.
- Quiñero Quiroga R. What is the real shape of extracellular spikes? *J Neurosci Methods*. 2009; 177:194–8. [PubMed: 18983872]
- Riehle A, Grun S, Diesmann M, Aertsen A. Spike synchronization and rate modulation differentially involved in motor cortical function. *Science*. 1997; 278:1950–3. [PubMed: 9395398]
- Sloper JJ, Hiorns RW, Powell TPS. Qualitative and Quantitative Electron-Microscopic Study of the Neurons in the Primate Motor and Somatic Sensory Cortices. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences*. 1979; 285:141.
- Suner S, Fellows MR, Vargas-Irwin C, Nakata GK, Donoghue JP. Reliability of signals from a chronically implanted, silicon-based electrode array in non-human primate primary motor cortex. *IEEE Trans Neural Syst Rehabil Eng*. 2005; 13:524–41. [PubMed: 16425835]
- Szarowski DH, Andersen MD, Retterer S, Spence AJ, Isaacson M, Craighead HG, Turner JN, Shain W. Brain responses to micro-machined silicon devices. *Brain Res*. 2003; 983:23–35. [PubMed: 12914963]
- Thorp CK, Steinmetz PN. Interference and Noise in Human Intracranial Microwire Recordings. *Ieee Transactions on Biomedical Engineering*. 2009; 56:30–6. [PubMed: 19224716]
- Thorsen F, Erslund L, Nordli H, Enger PO, Huszthy PC, Lundervold A, Standnes T, Bjerkvig R, Lund-Johansen M. Imaging of experimental rat gliomas using a clinical MR scanner. *Journal of Neuro-Oncology*. 2003; 63:225–31. [PubMed: 12892228]
- Turner JN, Shain W, Szarowski DH, Andersen M, Martins S, Isaacson M, Craighead H. Cerebral astrocyte response to micromachined silicon implants. *Exp Neurol*. 1999; 156:33–49. [PubMed: 10192775]
- Vetter RJ, Williams JC, Hetke JF, Nunamaker EA, Kipke DR. Chronic neural recording using silicon-substrate microelectrode arrays implanted in cerebral cortex. *IEEE Trans Biomed Eng*. 2004; 51:896–904. [PubMed: 15188856]
- Ward MP, Rajdev P, Ellison C, Irazoqui PP. Toward a comparison of microelectrodes for acute and chronic recordings. *Brain Res*. 2009; 1282:183–200. [PubMed: 19486899]
- Williams JC, Hippensteel JA, Dilgen J, Shain W, Kipke DR. Complex impedance spectroscopy for monitoring tissue responses to inserted neural implants. *Journal of neural engineering*. 2007; 4:410–23. [PubMed: 18057508]

- Williams JC, Rennaker RL, Kipke DR. Long-term neural recording characteristics of wire microelectrode arrays implanted in cerebral cortex. *Brain Res Brain Res Protoc*. 1999; 4:303–13. [PubMed: 10592339]
- Wiltchko AB, Gage GJ, Berke JD. Wavelet filtering before spike detection preserves waveform shape and enhances single-unit discrimination. *J Neurosci Methods*. 2008; 173:34–40. [PubMed: 18597853]
- Zhang J, Riehle A, Requin J, Kornblum S. Dynamics of single neuron activity in monkey primary motor cortex related to sensorimotor transformation. *J Neurosci*. 1997; 17:2227–46. [PubMed: 9045746]

Figure 1.

Overall model infrastructure. (A) A volume conductor model of a rat head with an implanted microelectrode of various contact sizes were coupled with a neural source model of a pyramidal cell to approximate the extracellular recording of action potentials. The peak-to-peak recording amplitude for each electrode size was calculated from these theoretical waveforms. (B) Recording noise was estimated by considering both biological and thermal noise sources. Biological noise was approximated by placing hundreds of neurons around the recording electrode. Thermal noise was calculated using the Johnson-Nyquist formula and parameterization of an impedance model using *in vitro* and *in vivo* impedance measurements. (C) The peak-to-peak recording amplitude calculated in (A) and the recording noise estimated in (B) were used to calculate the signal-to-noise ratio for each electrode size.

Figure 2.

Coupled FEM-neuron model of extracellular neural recording. (A) FEM of a rat head consisting of four concentric spheres representing gray matter, CSF, the skull, and the scalp. The FEM also contained the explicit representation of a recording electrode implanted in the cortex along with a 20 μm thick encapsulation layer surrounding the electrode. FEMs were generated for microelectrode sizes of 177, 413, 703, and 1250 μm^2 . (B) Multi-compartment model of layer V pyramidal cell consisting of several different ion channel types. An action potential was generated in the model neuron by incorporating excitatory synaptic inputs at the apical dendrites. The current densities at various time points during action potential generation are shown above. (C) The FEMs in (A) and the neuron model in (B) were coupled using the solution technique described in 2.3.1 to simulate extracellular voltage recordings for microelectrode contact sizes of 177, 413, 703, and 1250 μm^2 .

Figure 3.

Impedance model for the thermal noise estimates. (A) Impedance model of chronically-implanted microelectrodes consisting of both electrode and tissue components. The electrode component is a CPE representing the electrode-electrolyte interface. The tissue component represents the tissue response that occurs near the electrode as part of the foreign-body reaction. This impedance model is described in 2.2.1. (B) One example of the impedance measured *in vivo* for the cortical microelectrodes considered in this study (black line and circle markers) and the contribution of the individual model components in (A) to the overall electrode impedance spectrum (blue = electrode component, green = tissue component, red = complete model). (C) Impedance spectra of the four electrode sizes examined in this study using the average electrode and tissue model parameters from the *in vitro* and *in vivo* impedance data (see 3.2.1). In (B) and (C), the abscissa represents the real or resistive component of the electrode impedance and the ordinate represents the imaginary or reactive (capacitive) component of the electrode impedance. Each circle marker represents the impedance at a specific frequency ranging from 100 Hz to 10 kHz.

Figure 4.

Recording amplitude estimation and biological noise model. (A) To estimate the signal amplitude for the extracellular recording of single-unit activity, a model neuron was placed with its soma 50 μm away (along the z-axis) from the center of the recording contact. The image in A shows a log scale of the transmembrane currents (i_m) in nanoamperes for each neural compartment during the peak of the action potential at the axon hillock. (B) An example of one of the neuron distributions used to simulate biological noise. The neuron highlighted in red represents the position of the neuron in A from which signal amplitudes were estimated. The plot on the far right shows one of the neuron distributions used in the model analysis for a neuronal density of 9.5×10^6 neurons/ cm^3 . Each dot represents the location of the soma for the 325 individual model neurons. As described in 2.2.2, the ROI containing the model neurons was translated a distance of 50 μm normal to the electrode surface.

Figure 5.

Simulated extracellular recordings. (A) Simulated extracellular neural recording for a contact surface area of $703 \mu\text{m}^2$ shown with and without the estimated thermal noise. (B) Simulated extracellular neural recording with and without one example of the estimated biological noise. (C) Simulated extracellular neural recording with both thermal and biological noise. (D) Action potential recording amplitude as a function of contact surface area. The signal amplitudes were estimated with the soma of the neuron model located a distance of $50 \mu\text{m}$ from the center of the recording electrode. (E) Standard deviations of thermal, biological, and total recording noise as a function of electrode size. (F) Recording SNR as a function of contact surface area combining the estimates of recording amplitude and total noise from (D) and (E), respectively. For (D) and (F), the percent change in the recording amplitude and SNR relative to a microelectrode size of $177 \mu\text{m}^2$ are shown in the right-hand ordinate.

Figure 6.

The effects of band-pass filter settings on recording quality. Column (I) represents band-pass filter settings with a variable high-pass cutoff frequency ($f_{\text{high}} = 10 - 1000$ Hz) and a fixed low-pass cutoff frequency ($f_{\text{low}} = 5$ kHz). Column (II) represents bandpass filter settings with a fixed high-pass cutoff frequency ($f_{\text{high}} = 450$ Hz) and a variable low-pass cutoff frequency ($f_{\text{low}} = 1 - 10$ kHz). (A) Plots of the filter gain illustrating the ranges of cutoff frequencies examined in columns (I) and (II). (B) Peak-to-peak amplitudes of the action potential recorded at the specific filter settings. Recording amplitudes were estimated for a model neuron with its soma located $50 \mu\text{m}$ normal to the center of a $703 \mu\text{m}^2$ recording contact. (C) Thermal (red line), biological (blue line), and total recording noise (green line) for the specified filter settings. (D) SNR calculated from the signal and noise estimates in (B) and (C). (E) Voltage recordings for a selected set of band-pass filter parameters showing the influence of filter settings on the shape and amplitude of the action potential recordings.

The filter used in this analysis was a Butterworth filter with a 2-pole high-pass filter and a 2-pole low-pass filter.

Table 1

Variability in noise estimates.

		Noise Standard Deviation (μV)	Percent Change (%)
Thermal Noise ^a			
Impedance	Z_{avg}	6.20	N/A
	Z_{low}	3.45	-44
	Z_{high}	6.53	5
Bandwidth (Hz)	450–5000	6.20	N/A
	100–10,000	8.37	35
Biological Noise ^b			
Neuron Density (neurons/cm ³)	9.5×10^6	10.2	N/A
	2.4×10^6	3.86	-62
Firing Rate (Hz)	20	10.2	N/A
	5	4.00	-61
Bandwidth (Hz)	450–5000	10.2	N/A
	100–10,000	17.7	75

^a Thermal noise estimates for variable impedance conditions and recording bandwidths. The parameters for the three impedance conditions are described in 3.2.2.

^b Biological noise for different neuron densities, firing rates, and recording bandwidth. In both *a* and *b*, the estimated noise standard deviation and the percent change are shown. All of the values reported in *a* and *b* were for a microelectrode surface area of $703 \mu\text{m}^2$.