Recovery of Slow Potentials in AC-Coupled Electrocorticography: Application to Spreading Depolarizations in Rat and Human Cerebral Cortex

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INTRODUCTION

Following his initial description of “spreading depression of activity in the cerebral cortex” (Leão 1944), Leão described with DC-coupled amplifiers a negative slow voltage variation lasting 1–2 min that accompanied the spontaneous depression of cortical activity (Leão 1947). Subsequent work showed that this negative DC shift—the largest extracellular voltage change observed in the brain, ≤20 mV in cortex and 40 mV in hippocampus (Herreras and Somjen 1993)—is the signature of mass neuronal/astrocytic depolarization underlying the spreading depression phenomenon (Grafstein 1956; Hansen and Zeu-

then 1981). Spreading depolarizations arise spontaneously and repetitively following acute cortical injury in animals, including both focal ischemia and trauma. Since the late 1970s, spreading depolarizations have been studied with DC-coupled recordings as a mechanism of lesion maturation in the ischemic penumbra (Strong and Dardis 2005) and have been hypothesized as a pathologic mechanism in both acute brain injury and migraine in humans (Hansen and Lauritzen 1984; Lauritzen 1985). Depolarizations occurring in the ischemic penumbra are often termed “peri-infarct depolarizations” and differentiated from spreading depressions in normally perfused cortex. For the purposes of this study, both are referred to generically as spreading depolarizations.

In recent years, clinical studies have confirmed that spreading depolarizations do in fact occur as a common sequela of acute brain injury in man, including trauma and ischemic and hemorrhagic stroke (Dohmen et al. 2008; Dreier et al. 2006; Fabricius et al. 2006; Strong et al. 2002). In these studies, linear electrode strips are placed on the cerebral cortex in patients requiring neurosurgical intervention for ischemic/hemorrhagic stroke or traumatic brain injury. Electrocorticographs (ECoGs) are recorded from platinum electrodes with clinically standard, AC-coupled amplifiers. With the use of 0.02-Hz high-pass cutoff settings, it has been possible to identify multiphasic slow potential changes (SPCs) with an initial negative component and 0.06- to 3.0-mV amplitude (Fabricius et al. 2006). These SPCs recorded with AC-coupled amplifiers (AC-SPCs) reflect the SPCs commonly recorded with DC-coupled amplifiers (DC-SPCs) in animal experiments as the hallmark of tissue depolarization (Hartings et al. 2006). Depolarizations are thus identified in human ECoGs as AC-SPCs (with or without simultaneous depressions of spontaneous activity) occurring at adjacent electrodes with apparent propagation velocities (1–5 mm/min) consistent with spreading depolarization. With these methods, spreading depolarizations have been identified as occurring in roughly 50–70% of patients monitored (Dohmen et al. 2008; Dreier et al. 2006; Fabricius et al. 2006).

Visual identification of AC-SPCs is thus useful for clinical confirmation of tissue depolarizations. However, due to distortions introduced by the amplifier, AC-coupled recordings are unsuitable for assessment of the actual cortical SPC signal corresponding to a depolarization wave, whose frequency content extends far below 0.02 Hz. Specifically, AC-coupled amplifiers introduce phase and amplitude distortions that are dependent on the complex and varying spectral composition of...
the input signal, which is unknown. This effect is directly dependent on the specific filtering characteristics of the amplifier and is critical for low-frequency inputs located near or below the transition band of the high-pass filters. It is further possible that very low frequency components of an input signal are completely attenuated so that no trace can be detected or distinguished from noise in the AC-coupled recording. These considerations constitute a severe limitation for the use of AC-coupled ECoG to study spreading depolarizations, since there is diagnostically important information in the full-band waveforms that may be lost. Specifically, depolarizations associated with progressive ischemic damage are prolonged, with more persistent negative DC shifts, than those occurring in healthy cortex (Dreier et al. 1998; Mies 1997).

In the present study we investigate the relationship between the DC-SPCs of spreading depolarizations and their manifestations in AC-coupled recordings. In particular, we develop a signal processing method to recover low-frequency components from AC-coupled recordings, allowing the approximate reconstruction of full-band, DC-coupled recordings. The multiphasic AC-SPCs from clinical recordings are analyzed and signal processing methods are applied to show the full-band DC waveforms of spreading depolarizations from a series of in vivo patient recordings.

M E T H O D S

Signal analysis and recovery

CHARACTERIZATION OF THE SYSTEM TRANSFER FUNCTION. The following procedure was applied to each of two different setups for AC-coupled ECoG recording, one using the GT205 amplifier (Guger Technologies, Graz, Austria) and the other using the Dual Bioamp (model ML135, ADInstruments, Sydney, New South Wales, Australia). All calculations were performed in Matlab 7.2.0.232, the Signal Processing Toolbox version 6.5, and Filter Design Toolbox version 3.4 (The MathWorks, Natick, MA). Algorithm details are presented in the Technical Appendix.

A test signal from a programmable signal generator was injected into the front end of each AC-coupled bioamplifier. Bioamplifier settings were the same as those used for rat and human ECoG recordings (see following text): gain, 1,000; low-pass filter cutoff, 100 Hz; and high-pass filter cutoff, 0.02 Hz. The test signal consisted of eight negative unipolar cosine periods (i.e., each peak is at the zero baseline so the entire waveform is negative) of increasing durations and three positive unipolar cosine periods (i.e., each peak is at the zero baseline so the entire waveform is positive) of increasing durations. The full test sequence lasted about 3.5 h, given that triangular decreasing ramps (20, 120, and 600 s) and three positive unipolar cosine periods (i.e., each peak is at the zero baseline so the entire waveform is negative) of increasing durations and three positive unipolar cosine periods (i.e., each peak is at the zero baseline so the entire waveform is positive) of increasing durations. A zero-pole analysis confirmed this problem, locating the source of instability as a single pole outside the unit circle. A modified, stable version of this reciprocal was calculated by reflecting the root of the z-domain polynomial to a value inside the unit circle. An interactive filter design tool (Idatool, Matlab Signal Processing Toolkit) verified this algebraic manipulation. Visualization of the magnitude and phase delay responses of the model filters confirmed that the modified reciprocal mirrored closely, but not identically, both the magnitude and phase delay responses of the system transfer function (see Technical Appendix). For subsequent computations, this modified reciprocal was implemented as a digital filter having the same structure as the system transfer function. This inverse filter was then used for off-line processing of human and rat AC-coupled ECoG recordings to reconstruct the morphology of the low-frequency components present in the actual input, before they were attenuated by the AC-amplifiers.

Animal preparation and recordings

Six male Sprague–Dawley rats weighing 275–300 g were used in the experiments. Experiments were performed at the Walter Reed Army Institute of Research (WRAIR) or Charité University Medicine Berlin and all procedures were approved by the Animal Care and Use Committees at the respective institutions. Research was conducted in compliance with the Animal Welfare Act, the National Institutes of Health Guide for the Care and Use of Laboratory Animals (National Research Council), and other U.S. statutes and regulations relating to animals and experiments involving animals.

For surgical procedures, anesthesia was induced with 5% isoflurane delivered in oxygen, maintained at 2% during surgery, and reduced to 1.5% throughout experimental monitoring. Core body temperatures were maintained at 37°C by a homeothermic heating blanket. After catheterization of the femoral vein, rats were mounted in a stereotaxic frame and the skull was exposed by midline scalp incision and retraction of the right temporal muscle. The skull was thinned with a dental drill and removed by scalpel over an area 10 × 5 mm, extending from midline to the lateral ridge, and from lambda to bregma, for placement of electrodes. A second small craniectomy (~2 mm²) was made near the frontal pole (4 mm anterior, 2 mm lateral to bregma) for inducing spreading depolarizations. Small incisions were made in the dura at both craniectomies and the exposed brain was kept moist with physiologic saline. Depolarizations were induced by 30-s application of 2 M KCl to the frontal craniectomy. In two experiments, depolarizations were induced by cortical pinprick with a 25-g needle through one of five burr holes in the skull. Burr holes were drilled near the frontal pole of the brain and along the temporal bone (see Fig. 2).

Rat ECoG recordings were obtained from custom-made platinum electrode discs identical to those used in clinical recordings (2.3-mm-
diameter exposed platinum; Wyler, Ad-Tech Medical, Racine, WI). Two electrodes were placed on the dura and held in place relative to the adjacent skull with bone wax (see Fig. 2). Monopolar and bipolar ECoG recordings were made with the GT205 (Charité, n = 3 rats) or ML135 (WRAIR, n = 3 rats) AC-coupled amplifiers, digitized at 200 Hz with a Powerlab 16/SP, and recorded with Chart 5 software (ADInstruments). Band-pass settings were 0.02–100 Hz. Signals were also input to a Grass Model 15 (WRAIR: model 15A12, Grass Instruments, Natick, MA) or BrainAmp (Charité: BrainProducts, Munich, Germany) amplifier for simultaneous DC-coupled recordings. A sintered Ag/AgCl pellet electrode placed subcutaneously in the neck served as reference for monopolar recordings. Animals were killed at the end of experiments by intravenous injection of an air bolus or 2 M KCl.

Clinical electrocorticography

Electrocorticography data were obtained from five patients with aneurysmal subarachnoid hemorrhage at Charité University Medicine Berlin. The research protocol was approved by the local ethics committee and was conducted in compliance with the Declaration of Helsinki. Procedures for placement of subdural electrode strips have been described previously in detail (Fabricius et al. 2006; Strong et al. 2002). Briefly, after a clinical decision had been made that surgery was required for aneurysm clipping, written informed consent to participate in the study was obtained. During surgery, an ECoG electrode strip was placed on the cortex accessible by the craniotomy. The lead wires were tunneled under the skin and exteriorized through a stab wound. ECoG recordings were then initiated after transfer to the intensive care unit. Details of clinical care during ECoG monitoring are described in detail in Dreier et al. (2006). ECoG was terminated and electrode strips were removed after 5 days of recording or when patients were withdrawn from sedation.

ECoG recordings were made from a linear subdural strip consisting of six electrodes, with 10-mm spacing between electrodes and 2.3 mm of exposed platinum per contact (Wyler, Ad-Tech Medical). Data were acquired continuously from five active electrodes connected in sequential bipolar fashion, to yield four recording channels. Isolated ground was provided by the remaining electrode. Recordings were made with a GT205 (ADInstruments) AC-coupled amplifier with 0.02- and 100-Hz band-pass settings. Data were digitized at 200 Hz with a Powerlab 16/SP A/D converter and recorded with Chart 5 software (ADInstruments).

RESULTS

Complex SPCs are superpositions of simple SPCs

Figure 1 shows representative examples of spreading depolarizations recorded with AC-coupled ECoG from cerebral cortex in three patients (Fig. 1, A–C, respectively). Spreading depolarizations are identified by the sequential occurrence of SPCs on adjacent recording channels, with propagation velocities consistent with Léao’s spreading depression (Fabricius et al. 2006). Note, however, that the morphologies of SPCs are heterogeneous. In Fig. 1A, for instance, simple SPCs occur as predominantly biphasic events with slow apparent propagation velocities (Fig. 1A; 1 mm/min). Phase reversals on adjacent channels sharing a common electrode allow identification of the active site of depolarization. In this case, simple SPCs occur at each electrode (1–4) without temporal overlap. In other cases, however, complex SPCs occur with multiphasic waveforms (Fig. 1, B and C). In these cases, apparent propagation velocities are faster (4 and 5 mm/min, respectively), such that SPCs appear to occur on adjacent electrodes with temporal overlap.

To explain the heterogeneity of SPC waveforms and propagation velocities, we hypothesized that complex SPCs result from the temporal overlap of depolarizations occurring at both electrodes linked in a single channel, resulting in the superposition of simple SPC waveforms. To test this hypothesis, we made bipolar ECoG recordings from two electrodes in the rat using the same platinum disc electrodes used in human recordings. Depolarizations were elicited at different points spanning 0 to >90° relative to the axis of the electrodes to study the dependence of depolarization waveforms in bipolar recordings on 1) the orientation (direction) of the spreading wavefronts relative to the electrodes and thus 2) the relative timing of depolarization at each electrode linked in a bipolar channel (Fig. 2).

Monopolar recordings revealed stereotyped simple SPC waveforms (negative, positive, negative) at each electrode, regardless of the location at which depolarizations were elicited (Fig. 2, rows 2 and 3). However, bipolar recordings of the same events showed more complex and varying morphology that is explained by 1) the relative times at which the depolarization waves arrived at each electrode and 2) the resulting difference in summation of component waveforms. For instance, in the wave recorded from elicitation at site 2, after the positivity at electrode A, a second positivity occurs in the bipolar recording from the initial negativity (sign reversed) occurring at electrode B. Note the similarity of this recording to channel A in Fig. 1B. When depolarizations are elicited at site 3, with less delay between the waves’ arrivals at the two electrodes, electrode A’s positivity and B’s negativity sum in a single bipolar positivity. When depolarization is elicited at site 5, the time relation at the two electrodes is precisely reversed and the opposite bipolar waveform is observed. Thus the complex and varying morphology of SPCs in bipolar recordings is likely attributable to the relative timing of depolarization occurrence at each participating electrode and the variable superposition of simple SPC waveforms that results.

Recovery of low-frequency components from AC-coupled recordings

Simple SPCs recorded with AC-coupled amplifiers reflect severe distortions of the full-band potentials of depolarizations (Hartings et al. 2006). These distortions are introduced by the analog high-pass filters found in AC-coupled amplifiers, which have neither constant phase delay nor constant magnitude response in the high-pass transition region and thus alter the morphology of the low-frequency components in the output signal. Figure 3 illustrates this case by showing the responses of two different amplifiers to various synthetic low-frequency test signal inputs. The monophasic inputs result in multiphasic outputs with attenuated amplitude. The distortion effect is dependent on both the amplifier and the input frequency.

Figure 4 outlines the steps in our approach to correct the morphological distortions introduced by the high-pass filter of a specific amplifier and to recover close approximations of the original input, based solely on the recorded waveforms and characterization of the AC-coupled amplifier. First, the behavior of the amplifier was characterized by injecting synthetic test inputs and recording the outputs (Figs. 3 and 4A). The transfer
function of the amplifier was then implemented in a digital filter, such that it could duplicate the output of the analog amplifier (Fig. 4B). Based on this characterization, we synthesized an inverse digital filter that approximated the reciprocal of the amplifier transfer function within the low-frequency band. This inverse filter could then be applied to AC-coupled recordings as a digital signal processing tool, to reverse the distortions introduced by the amplifier and to recover the original input signal.

We first tested and refined the recovery procedure using the synthetic test data (Fig. 4C). Subjectively, we observed recovery of accurate morphology for most test deflections but the lowest frequency elements: zero frequency (absolute DC level) and flat linear trends. Figure 5A shows test examples. Spectral comparison of the input signals and those recovered with inverse filtering confirmed these results (Fig. 5D). Without further alteration of the inverse filter, we matched DC-coupled recordings from rats with simultaneous AC-coupled recordings of the same events, processed off-line by the inverse filter (Fig. 4D). After this validation, the inverse filter could then be applied to human AC-coupled ECoG to recover the approximate full-band waveforms of spreading depolarizations (Fig. 4E). All of these procedures (Fig. 4, A–D) were performed for each of the two AC-coupled amplifiers (GT205 and ML135) and similar results were obtained. For simplicity, only results for the amplifier used clinically are presented (GT205).

Application of inverse filtering for recovery of full-band SPCs from AC-coupled recordings

To determine whether full-band SPCs could be recovered from recordings made with AC-coupled amplifiers, we made recordings of spreading depolarizations from rat cortex by splitting the input from the same electrode into both a narrowband (0.02-Hz high-pass) AC-coupled amplifier and a full-band DC-coupled amplifier (Fig. 4D, schematic). Representative examples of spreading depolarizations recorded with both amplifiers are shown in Fig. 5B. Note the markedly disparate
morphologies of the AC-coupled recordings in relation to the full-band signals. When the inverse filter is applied to the AC-coupled recordings, however, the resulting signal reconstructions closely match the full-band recordings of these same events (Fig. 5B). For 20 depolarizations recorded in three rats, the durations of signal negativity in the full-band recordings and the reconstructed signals were highly correlated ($R^2 = 0.97$; $P < 0.001$).

Spreading depolarizations that occur under conditions of metabolic compromise, such as peri-infarct depolarizations, are longer lasting than depolarizations in healthy cortex due to prolonged repolarization phases. These lower-frequency waves are subject to the most severe amplitude attenuation by AC-coupled amplifiers (see Fig. 3). To determine whether the inverse filtering technique is capable of recovering these prolonged depolarizations, we applied ouabain to the cortex to extend the duration of repolarization. As shown in Fig. 5C, recovery of these prolonged depolarizations was also possible, albeit with some uncertainty about the lowest frequencies and absolute DC levels.

Comparison of spreading depolarizations in rat cortex and human cerebral cortex

The inverse filter was then applied to simple SPCs recorded from human cortex with AC-coupled amplifiers in five pa-
patients. These patients suffered aneurysmal subarachnoid hemorrhages and underwent continuous ECoG monitoring with subdural electrode strips following aneurysm clipping. Figure 6, A and B shows representative examples of simple SPCs from two patients and the recovery of full-band SPCs after processing the recorded ECoG with the inverse filter. As observed in rat recordings, the full-band reconstructions differ dramatically from the AC-coupled simple SPCs. Furthermore, the full-band SPCs from human cortex exhibit the hallmark characteristics of spreading depolarizations recorded with DC-coupled amplifiers in animals. These include a rapidly developing negativity and a positive potential overshoot following repolarization.

In total, we assessed 117 simple AC-SPCs recorded from 71 separate spreading depolarization events in five patients at 17 different electrodes. All AC-SPCs and full-band reconstructions are shown in Fig. 6C. Rat AC-SPCs and reconstructions are shown in Fig. 6D for comparison (n = 20 in three rats). Characteristics of the human potentials were quantified for each of the 17 recording sites (Fig. 7). The mean peak-to-peak amplitude of the human AC-SPCs was 3.0 mV (SD 1.4), which did not significantly differ from the rat AC-SPCs (2.8 mV, SD 0.9). However, the amplitudes and durations of the corresponding reconstructions of human SPCs were significantly greater than those of the rat (P values <0.001, t-test). For humans, the mean duration of negativity below baseline was 1 min 47 s (SD 26 s). The amplitude of the negativity was 6.5 mV (SD 3.2) and peak-to-peak amplitude was 10.1 mV (SD 4.2). In rats, full-band reconstructions had durations of 45 s (SD 9 s), negative amplitudes of 2.6 mV (SD 0.8), and peak-to-peak amplitudes of 4.2 mV (SD 1.3).

DISCUSSION

Understanding the clinical significance of slow potentials in the human brain requires reliable recording techniques. The first large series of patients in which the slow potentials of spreading depolarizations were monitored has been accomplished with bipolar AC-coupled recordings from serially linked subdural electrodes (Dohmen et al. 2008; Dreier et al. 2006; Fabricius et al. 2006). This method is robust, uses current neurosurgical techniques, commercially available and standard neurophysiological equipment, and can be implemented with minimal training of neurosurgeons and clinical neurophysiologists. A drawback, however, is the frequency limitation imposed by high-pass filters (0.02 Hz) during data acquisition, which precludes proper assessment of the waveforms and durations of the DC shifts that are the signature of cortical depolarizations. Here, we have largely overcome this limitation by applying digital signal processing techniques to recover slow potentials down to 1 mHz. Using inverse digital filters that reverse the effects of high-pass filtering, we have recovered the approximate full-band DC waveforms of depolarization events. In doing so, we 1) provide evidence that AC-SPCs propagating with depressions of fast ECoG activity reflect depolarizations as recorded with DC amplifiers in animals; 2) provide a quantitative description of the full-band, slow potential waveforms of depolarizations in human cerebral cortex; 3) provide a means to assess the durations of depolarizations, as reflected in negative DC shifts, from AC-coupled recordings; and 4) illustrate a particular technique for the recovery of very low frequency events from AC-coupled recordings.
applied to human AC-coupled ECoG, digital inverse filtering recovered slow potentials similar in morphology to the DC shifts of spreading depolarizations in animals, supporting the conclusion that spreading AC-SPCs represent depolarization phenomena in human cortex (Fabricius et al. 2006). The unprocessed AC-SPCs had similar morphology and amplitude in rat and man, but differed in the longer duration of human AC-SPCs. Accordingly, the reconstructed DC-SPCs were of larger amplitude in man than those in rat, since the DC waveforms, to a first-order nonquantitative approximation, are integrals of the AC-SPC signals (Fabricius et al. 2006; Harnings et al. 2006). Physiologically, the larger amplitude of human DC-SPCs compared with that of the rat may result from the longer DC potential negativity in human cortex: because the longer duration creates a greater wavelength of the depolarization front (e.g., human: 1.78 min × 3 mm/min = 5 mm; rat: 0.75 min × 3 mm/min = 2.25 mm), a larger area of cortex is simultaneously depolarized. The assumption of similar propagation velocities for rats and humans is supported by both in vivo (mean 3.3 mm/min; Fabricius et al. 2006) and in vitro (mean 3.1 mm/min; Gorji et al. 2001) human recordings. The basis for a longer-duration DC negativity in man is unknown, but the values reported here are consistent with those from recent DC recordings of spreading depolarizations in human cortex in vivo (Dreier et al. 2009). It is possible that differences in conductivity of cortex, pia mater, or surrounding media in rats versus humans contribute to differences in the durations of DC negativities recorded with subdural electrodes, when in fact the durations of neuronal depolarizations may be more similar. However, the durations of DC negativities recorded from human neocortical slices with microelectrodes (mean: 1.70 min; Gorji et al. 2001) are in agreement with values reported here, arguing against such effects. It is unknown how intracortical microelectrode recordings of spreading depolarizations relate specifically to recordings with subdural clinical electrodes, which have a large surface area of 4.2 mm². The effects of spatiotemporal averaging over this area, particularly compared with microelectrode recordings, are dependent on many factors including the depth, velocity, and duration of wave propagation, and deserve future study.

The objective of the present study begs the question of whether clinical data should not be directly acquired with DC amplifiers. One limitation to this approach is the polarizable nature of clinical subdural electrodes (Ikeda et al. 1998; Tallgren et al. 2005), which introduce substantial offset potential and baseline drift. Further low-frequency shifts are introduced as artifacts from the intensive care environment with frequent nursing and clinical interventions. These problems can be managed in two ways: by setting up a very wide voltage recording range (>500 mV) coupled with high-resolution A/D converters, to mitigate the loss of amplitude resolution, or by applying procedures to reset the DC level, resulting in some form of high-pass filtering. Furthermore, to visually review such recordings, high-pass filtering at some level is necessary to generate a stable, “readable” baseline. Insofar as stable recording conditions can be achieved, DC amplification would be the preferred method to record infraslow phenomena. Alternatively, we have shown that it is possible to recover very low frequency waveforms from AC-coupled ECoG data acquisition setups, effectively extending the working bandwidth of the AC-coupled amplifier. Thus our approach can be viewed as
a complementary technique to achieve an endpoint similar to that of DC recordings, without the use of DC amplifiers proper. This approach takes advantage of the mature market of clinical AC-amplifiers and the vast pool of expertise available for their clinical use, while avoiding some difficulties of deploying DC recording systems in an intensive care setting.

A second consideration in equipment and methodology is the choice of montage. Heretofore, we have used a sequential bipolar linkage of electrodes into our ECoG recording channels. This montage was chosen as protection against a faulty reference electrode and to optimize detection of spreading depressions of high-frequency ECoG activity (Van Harreveld and Stamm 1951). The disadvantage is that SPCs often occur with temporal overlap on adjacent electrodes connected in a single recording channel, resulting in a complex SPC (Fig. 1, B and C). Since the full-band waveform of a depolarization is meaningful only as a monopolar (e.g., referential) signal, complex SPCs introduce additional obstacles for signal recovery. Thus to combine robust recordings of high-frequency ECoG activity with capture of monopolar SPCs, we recommend montages that allow derivation of both bipolar and monopolar recordings. It is important to note that bipolar recordings with superposition of SPCs from different electrodes are identified here only as one definitive source of waveform complexity—one that warrants decomposition in monopolar derivations. Biologic sources may additionally contribute to nonstereotyped SPC morphologies that may be present even in monopolar recordings. For instance, depolarization waves may propagate nonuniformly in superficial and deep layers of cortex and result in varied waveforms recorded by surface electrodes (Richter and Lehmenkühler 1993).

Framing the problem of ECoG evaluation in the signal processing context yielded interesting, unexpected results with implications beyond our application. The gold standard of electroencephalographic (EEG)/ECoG evaluation is visual inspection. However, as shown in Fig. 3, a recorded signal is highly dependent on characteristics of the recording and signal conditioning equipment used, even when manufacturers describe similar specifications (e.g., 0.02-Hz high-pass filter cutoffs). Thus caution is particularly warranted when comparing waveforms recorded with different hardware/software near the transition band of the filter, as is commonly done, for instance, with delta-frequency waveforms (e.g., slow waves, triphasic waves) recorded with 0.5- or 1.0-Hz high-pass filters. This led ECoG

![FIG. 6. Recovery of full-band SPCs from rat and human cortex by inverse filtering. Top row: raw SPCs, down-sampled to 1 Hz, recorded with the AC-coupled GT205 amplifier. Bottom row: the same waveforms after processing with the inverse filter. All data were temporally aligned by the time of peak negativity of the inverse filtered waveforms. A and B: overlays of multiple SPCs (8 and 4, respectively) recorded in 2 different patients. All SPCs shown were recorded from the same ECoG channel in the respective patient. C: overlay of all 117 SPCs analyzed from human recordings. D: overlay of 20 SPCs recorded in the rat. Red lines illustrate averages of all traces.]

![FIG. 7. Comparison of spreading depolarization SPCs in rat and human cortices. Durations of full-band SPC negativities (left) were measured as the duration of potential deviation below the baseline averaged over 1 min preceding the SPC. Data show means and SDs.]

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variability in filter design is a common hurdle to collating large, multicenter data sets. However, using inverse filters developed specifically for each of two different amplifiers, here we were able to reconstruct the same common input signal from the two amplifier outputs. Thus a generalization of this signal enhancement procedure could be formulated so that a multiplicity of recordings from different instruments could be normalized and analyzed as if they originated from a homogeneous set of recording instruments. Inverse filtering is particularly effective in recovery of depolarization waves because these phenomena have an intrinsically high signal-to-noise ratio (SNR). When favorable SNRs are achieved in other neurophysiology applications, most of the limitations of the method will depend on implementation and off-line preprocessing details (signal duration and segmentation and windowing parameters).

Other researchers have used inverse filtering in the processing of EEG signals to detect spikes and epileptiform activity (Barlow 1980; Pfurtscheller and Fischer 1978), to estimate the spectral characteristics of the EEG (Dutt 1994), or to improve the detection of event-related activity or auditory-evoked potentials (Salomon and Barfod 1977; Wright et al.1990). Although DC recordings are more feasible in scalp EEG due to the use of Ag/AgCl electrodes, AC-coupled amplifiers are used in invasive subdural recordings to record the Bereitschaftspotential (“readiness potential”) preceding voluntary movements (Ikeda et al. 1999b) as well as ictal DC shifts (Gross et al. 1999; Ikeda et al. 1999a). Inverse filtering may greatly aid the characterization and interpretation of these potentials, particularly in the latter cases in which intracranial recordings are compared with scalp recordings. In summary, development of the inverse filtering procedure is a step aimed directly toward bridging the gap between AC- and DC-recording techniques. Future development should include on-line implementation of the inverse filter procedure to facilitate its use.

APPENDIX

Statement of the problem

Consider an ideal AC-recording system, complete and noise-free from the electrode and front-end electronics, the amplifier, and digitizer back end, to the final output signal as recorded. Let the discrete time series \( x(n) \), \( h(n) \), and \( y(n) \) be the potential difference at the electrode–tissue interface, the discrete transfer function, and the
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recorded signal, respectively. For all cases, \( n \) is the sample index and \( * \) denotes convolution in the time domain

\[
y(n) = h(n) * x(n)
\]  
(A1)

After \( z \)-transformation, \( Y(z), H(z), \) and \( X(z) \) are the complex frequency counterparts of the time domain terms of Eq. A1, so that

\[
Y(z) = H(z) \cdot X(z)
\]  
(A2)

\( H(z) \) comprises all the modifications (attenuation/amplification, phase-shifting, scaling, quantization, etc.) performed on \( X(z) \), such that they yield \( Y(z) \), and the dot operator denotes multiplication in the frequency domain.

**Equation A2** represents a measurement without error. \( Y \) is the recorded signal, the operator is unaware of \( H \) in an exact, quantitative sense, and \( X \) is the unknown electrode potential. It is possible to find \( G(z) \), the reciprocal or inverse of \( H(z) \), such that when applied to output \( Y(z) \), it yields the original input \( X(z) \)

\[
G(z) \cdot H(z) = 1 \land G(z) = \frac{1}{H(z)}
\]  
(A3)

\[
X(z) = G(z) \cdot Y(z)
\]  
(A4)

To recover the unknown input \( X \), we must know enough about \( H \) to be able to revert its effects by finding and applying a function \( G \) (Eqs. A3 and A4).

**Proposed solution**

The solution consists of three steps that use standard signal processing methods and algorithms (Hayes 1999; Hsu 1995; Ljung 1987; Lyons 1996; Steiglitz and McBride 1965; Stengel 1994). The first step is to characterize as accurately as possible the total transfer function \( H(z) \) of the recording system. The second step is to find \( G(z) \), the reciprocal of \( H(z) \). The last step is to implement a procedure to process recorded signals \( Y \) with the function \( G(z) \) to recover \( X \).

**Step 1: modeling the total system transfer function.** The first step is to obtain a pristine set of known input and output signals by which \( H(z) \) can be characterized. In the present study, a test signal from a programmable signal generator was injected into the front end of the AC-coupled amplifier. Using a positive rectangular pulse of 2-mV amplitude and 10-min duration, a linear model of the transfer function was estimated. Other test signals produced similar, but not better performing, transfer functions. A possible interpretation of this is that the rectangular pulse contained richer spectral information because it is the best (noisy) approximation to the integral of the unit impulse.

Under the assumption that the system is discrete, linear, and time-shift invariant, \( H(z) \) takes the form of a rational function

\[
H(z) = \frac{\sum_{k=0}^{p} b(k)z^{-k}}{1 + \sum_{k=1}^{q} a(k)z^{-k}}
\]  
(A5)

The polynomial sums in the denominator and the numerator, of order \( p \) and \( q \), respectively, can be expressed as products of their respective roots, \( \beta(k) \) and \( \alpha(k) \)

\[
H(z) = C \prod_{k=1}^{p} \left[ 1 - \beta(k)z^{-k} \right] \prod_{k=1}^{q} \left[ 1 - \alpha(k)z^{-k} \right]
\]  
(A6)

where \( C \) is a scaling factor. If the system is invertible there exists \( G(z) \) such that Eq. A3 is satisfied.

There are various methods to find or approximate \( \beta(k) \) and \( \alpha(k) \), the roots of the rational polynomials that define \( H(z) \). We used a direct estimation procedure, the Steiglitz–McBride iteration, as implemented in the Matlab Signal Processing Toolbox v6.5. Starting from this characterization of \( H(z) \), we designed a stable, causal, infinite impulse response (IIR) digital filter, so that all work on recorded signals could be done in the time domain. A second-order section, a transposed direct-form II implementation, was chosen to improve numerical stability; the coefficients were scaled so that the filter has near-unity gain and the total gain of the system is represented by the scalar value of \( C \). This approach simplifies computations and data management because any additional scaling (e.g., input and output not expressed in the same voltage units) does not require the modification of any filter coefficients. Finally, the IIR model of the amplifier was applied to the synthetic test signals and its output was compared with the recorded output of the amplifier itself.

Proceeding iteratively, we adjusted the order of the numerator and denominator until the digital filter could reproduce the output of the amplifiers with very high correlation (\( r = 0.99974, \text{CI} \pm 1.5 \times 10^{-5}, \text{a} < 1 \times 10^{-3} \)). A third-order model was chosen according to these empirical criteria, resulting in both \( p = 3 \) and \( q = 3 \). Visualization of the magnitude response and phase delay confirmed predominance of the high-pass filter behavior of the IIR (Fig. A1). Stability was also confirmed algebraically and via a zero-pole plot using an interactive filter design tool. Interestingly, a first-order model does not reproduce the full behavior of the total transfer function, despite being the order of the analog high-pass filters, in the two amplifier models tested (ADInstruments ML135 and g.Tec GT205). This suggests that other components (or processing steps, such as digitizing, software manipulation during data acquisition, downsampling, etc.) introduce additional modifications, irrespective of whether they are filtering, undesired attenuation, phase-shifting, or noise.

**Step 2: constructing the inverse filter.** From Eqs. A2 and A4 we see that

\[
G(z) = C^{-1} \prod_{k=1}^{p} \left[ 1 - \alpha(k)z^{-k} \right] \prod_{k=1}^{q} \left[ 1 - \beta(k)z^{-k} \right]
\]  
(A7)

is the reciprocal of the system transfer function \( H(z) \). However, direct implementation of \( G(z) \) as a digital filter by the procedure described for \( H(z) \) yields an unstable filter. The source of instability originated in a single-pole set outside the complex unit circle, as verified both algebraically and graphically, on a zero-pole diagram. This is not unexpected, since not all high-pass IIR filters are invertible. As a compromise, we defined \( G(z) \) by rescaling \( \beta(k) \) and \( \alpha(k) \) so that the poles and zeros are located within the unit circle on the complex plane. Thus \( G(z) \) will be only an approximate inverse of \( H(z) \); thus the trade-off for stability is renouncing an exact solution for the recovery of \( X \). Visualization of the magnitude response and phase delay confirmed that the profiles of \( G(z) \) mirror those of \( H(z) \), but with minor differences for very low frequencies (<1 mHz, as seen in Fig. A1). The approximate inverse filter was tested by applying it to the output \( Y \) that the amplifiers produced for known input test signals \( X \). The reconstructed waveforms were compared to the known input signals \( X \).

A consideration in the decision to derive a stable, causal, linear approximate inverse was the ultimate goal of producing a procedure that could be applied on-line and in real time—not only when data acquisition has been completed. The elementary approach described in these two steps assumes that the background noise is broadband, constant for all frequencies, and has low power (relative to the power of waveforms of interest).

**Step 3: implementation and processing of ECoG data.** The filter specification of \( H(z) \) has a sharp transition region with a \(-3 \text{dB} \) corner near 0.02 Hz. All input near or below this frequency will be subject to increasing attenuation and phase distortion, whereas input with spectral content above this transition band will be amplified with minimal distortion because the magnitude response and phase delay of the passband become flat. The transition zone of the high-pass filters...
modeled is very narrow relative to the bandwidth of the amplifier. Thus to improve the numerical stability of our approximations, we
designed them to operate on signals sampled at 1 Hz. In all cases
(including steps 1 and 2, presented earlier) we assumed inputs sam-
pled at 1 Hz.

To work with actual ECoG recordings, regardless of the sampling
rate at which they were acquired, we split them into two secondary
signals: one carrying frequencies $<0.5$ Hz (i.e., the standard EEG/ECoG band). The sub-
band splitting must be realized using zero-phase procedures, although
this is possible only off-line. On-line implementation will depend on
efficient filter banks, taking care that the minimal distortions are above
the operating range of the reconstruction procedure. The low-fre-
cquency secondary signal is down-sampled to 1 Hz, again using
zero-phase implementations. Then, the inverse filter specified by $G(z)$
is applied and its output is up-sampled back to the original sampling
rate, using an interpolation scheme that avoids further phase distor-
tions and that preserves the original number of data points. When this
reconstructed signal is added to the secondary high-frequency signal
(containing standard ECoG activity $>0.5$ Hz), the end result is a
bandwidth enhancement of the original AC-ECoG, with very low
frequency components, that approximates a full-band recording

$$X(n) \leftarrow F[b, a, X(n)] \cdot C$$

so that the $z$-transform of $F$ has the form of Eqs. A5 and A6, with
coefficient vectors $b$ and $a$, and $C$ is a gain constant.

3) Estimate coefficient vectors $b$ and $a$ by means of estimating function $S[X(n), Y(n), p, q]$. We used the Steiglitz–McBride iteration,
but any other method of estimating $n$th-order linear models of input–
output relations is also valid. As noted, $b$ and $a$ could be estimated
using matching intervals $X(n, \ldots, n+k)$ and $Y(n, \ldots, n+k)$, instead
of the entire time series

$$p \leftarrow 3 \quad \text{(define third-order estimates)}$$

$$q \leftarrow 3$$

$$[b, a] \leftarrow S[X(n), Y(n), p, q]$$

4) Implement $\hat{F}$ as a digital filter and apply it to test signal $X(n)$

$$Y'(n) \leftarrow \hat{F}[b, a, X(n)] \cdot C$$

5) Test for the difference between filtered signal $Y'(n)$ and original
amplifier output $Y(n)$ to be less than tolerance $tol$ and for both signals
to be highly correlated

$$Y(n) \approx Y'(n) \wedge Y'(n) - Y(n) < tol \wedge \rho = 1$$

6) If criteria are not satisfied, go back to step 3, produce new
estimates of $b$ and $a$, and iterate until criteria are satisfied. If criteria
are satisfied, function $\hat{F}$ is the chosen model of the total system
transfer function.

7) Define $\hat{R}$ as a function of $a$, $b$, and $Y(n)$, mapping onto $X(n)$. Note coefficient reversal $a$ and $b$

$$X(n) \leftarrow \hat{R}[a, b, Y(n)] \cdot C^{-1}$$

either by direct estimation (as in point 2) or by algebraic manipulation (reflection of roots within the stable region) of $b$ and $a$, such that

$$X(n) \leftarrow \hat{R}[\hat{a}, \hat{b}, Y(n)] \cdot C^{-1}$$

10) Implement $\hat{R}$ as a digital filter and apply it to test signal $Y(n)$,
which yields $X'(n)$, the recovered time series

$$X'(n) = \hat{R}[\hat{a}, \hat{b}, Y(n)] \cdot C^{-1}$$

To render the lowest frequency recovered independent of signal
length and to compare signals of different lengths, a sliding-window
implementation may be desirable. Let

$$m \leftarrow \text{length}[Y(n)]$$

$$w \leftarrow \text{window length}$$

$$W \leftarrow \text{window function}$$

$$X'(1, 2, \ldots, m) \leftarrow 0$$

Iterate over all values of $k = 1, 2, \ldots, m-w$

$$X'(k, \ldots, k+w) \leftarrow X'(k, \ldots, k+w) + \hat{R}[\hat{a}, \hat{b}, W[Y(k, \ldots, k+w)]]$$

Normalize $X'$ according to gain constant $C$ and window function

$$X' \leftarrow X' / C \cdot \sum_{i=1}^{w} W$$

11) Follow by comparison of $X'(n)$ against the known reference
signal to assess overall performance.

$X'$ is the recovered baseline with enhanced low-frequency com-
ponents. It can be up-sampled and added to a filtered version of the
original signal (suppressing all content $<0.5$ Hz), to generate an
enhanced version of the original input.

Innovative Methodology
In general, it is helpful to ensure that \( X(n) \) and \( Y(n) \) are expressed in values that correspond to the same physical units, so that \( C \) is the only constant governing the gain applied to the output.

**Performance and limitations of the method**

The recovered signals display morphology resembling that seen in full-band recordings. For example, rat AC–ECoG enhanced by inverse filtering recovers the typical morphology of SPCs and the waveforms show high correlation to those simultaneously recorded with DC-amplifiers. Even if the recorded signal is identical to the original input, enhancement of the AC–ECoG highlights epochs of low-frequency activity whose features are not evident in the AC–ECoG trace. This is useful because visual inspection is the main form of assessment of these data and because AC-amplifiers are ubiquitous in clinical practice.

Sensitivity to broadband and low-frequency noise could be an issue, particularly during intensive monitoring, because numerous sources of noise are present and it is a factor that was not systematically evaluated here. Nonetheless, signal enhancement following this method seems consistently feasible, even when subdural AC–ECoG is captured using polarizable electrodes (the human and rat recordings examined here used platinum electrodes), an advantageous feature considering that polarizable metallic electrodes—that are not ideal for DC-recording—are the standard for this type of invasive neuromonitoring.

In this contribution we applied inverse filtering because of the favorable signal-to-noise ratio and the relative simplicity of this method compared with that of other alternatives. The results demonstrated succeed in reconstructing spreading depolarization waveforms and their associated SPCs because of the intrinsically high signal-to-noise ratio of these events when recorded with subdural electrodes and the fairly accurate characterization of the system used to record them. The practical consequence is immediate: changes to parts, procedures, or components that also modify the total system transfer function require concomitant modification of the inverse filters used for signal recovery.

**REFERENCES**


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**DISCLOSURES**

A portion of the methods presented here have been submitted as an invention disclosure to the Henry Jackson Foundation for the Advancement of Military Medicine.

**REFERENCES**


