On Statistical Properties of Whole Nerve Cuff Recordings

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***Abstract*— Whole nerve cuff electrodes can record an electric signal generated by the superposition of single fiber action potentials (AP's). Using a simple stochastic model for the superposition of AP's, the statistical properties of nerve cuff signals are mathematically derived in this study. Consequences of common signal processing methods like rectification and time-averaging are also explained. The nerve cuff signals are found to be approximately identically, independently distributed Gaussian signals with zero mean and varying variance. The spectral properties of the cuff signals generated by single AP shape or different AP shapes are also addressed and investigated by examining the properties of the autocorrelation functions of the nerve cuff signals. The theoretical results were found to be in accordance with computer simulations and processing of actual recorded data.**

***Index Terms*— Action potentials (AP's), cuff electrode nerve recording, nerve signals, statistics.**

I. Introduction

SINCE a method for recording nerve activity by means of cuff electrodes was introduced by Hoffer [1] and Stein [2], the method has been extensively applied in neurophysiological and neural prosthesis research, e.g., [3] and [4]. Stein described the physical principles behind the method, however, not much theoretical work has been done toward explaining statistical properties of the recorded signals. Contributions presented in the present paper try to establish a basis for the application of advanced signal processing methods to the neurographic recordings. Some application examples could be, e.g., classification of nerve signals, optimal filtering and signal detection. Specifically, mathematical derivations of the statistical properties of nerve cuff signals are carried out, complemented by computer simulations, and some actual nerve cuff recordings are analyzed with respect to the theoretical results of the manuscript.

The electroneurogram (ENG) from a whole nerve results from superposition of electric potentials generated by active nerve fibers present in the nerve. Extracellular electric current flow generated by traveling action potentials (AP's) is restricted and confined by an insulating cuff, which is placed around the nerve. One or more electrode contacts along inner side of the cuff are then used to measure potential differences due to longitudinal resistive potential drops. Cuff electrode geometry and configuration have a filtering effect on the waveform of each recorded AP traveling through the cuff [5]. This filtered version of superimposed AP's generated by nerve fibers with similar axonal size distribution, thus, make up a signal recorded by whole nerve cuff electrode. The number of AP's in a fixed time window is a function of the firing frequency in active nerve fibers and also of the number of active fibers. For a constant number of active nerve fibers the number of recorded AP's is proportional to the rate of firing of the neurons (nerve activity), which for sensory fibers encodes stimulus intensity. The goal of signal processing is, thus, generally to derive a signal proportional to the nerve activity. It will be shown that the recorded nerve cuff signal is approximately independently identically distributed (i.i.d.) Gaussian signal with zero mean and varying variance and that the common signal processing method of rectifying the recorded signal and averaging it is proportional to the square root of number of AP's present in a fixed time window. Furthermore, it will be shown that the autocorrelation function of the nerve cuff signal is primarily determined by the single AP shape, and is a scaled version of the single AP autocorrelation function. In case of several different AP shapes, the autocorrelation function will be a weighted average of the different single AP autocorrelation functions.

Manuscript received September 24, 1998; revised April 30, 1999. This work was supported by the Danish National Research Foundation and The Danish National Research Council. *Asterisk indicates corresponding author.*

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Publisher Item Identifier S 0018-9294(99)07416-9.

II. Methods

A. Mathematical Derivation of Statistical Properties

It is assumed that the signal is analyzed in a finite, fixed length time window $t \in [0, T]$ and results from superposition of N AP's, each having length $L \ll T$

$$s(t, \boldsymbol{t_{01}}, \ldots, t_{0N}) = \sum_{i=1}^{N} \mathrm{AP}(t - t_{0i}) \tag{1}$$

where $\mathrm{AP}(t)$ has a zero mean, and $\boldsymbol{t_{0i}}$ are uniformly distributed random variables on interval $[0, T-L]$ that determine positive shift of each AP. Only one single AP shape is assumed to be summed in this simple model, and $\mathrm{AP}(t)$ represents voltage as a function of time. $\mathrm{AP}(t)$ is deterministic, but signal s is random due to random shifts $\boldsymbol{t_{0i}}$ (s is, thus, a stochastic process). Each given set of values for the shifts $\boldsymbol{t_{0i}} = t_{0i}$ represents a single realization of the stochastic process $s(t)$. N can be arbitrarily large, causing multiple overlaps of AP's.

The central-limit theorem [6] is used to prove a Gaussian probability density function for signal $s(t)$. Here, we also

recall the value of the ratio

$$\frac{\sqrt{E\{w^2\}}}{E\{|w|\}} = \sqrt{\frac{\pi}{2}} \approx 1.2533 \tag{2}$$

for Gaussian random variable w. $E\{-\}$ stands for the statistical expected value.

B. Computer Simulations

A triphasic compound AP (CAP) of duration 1 ms was extracted from a porcine pelvic nerve cuff recording following the threshold current stimulation of the sacral root S3 [7]. It, therefore, resulted from a superposition of several AP's that probably belonged to the nerve fibers with same/similar fiber diameters. The recorded CAP was, thus, a representative of a small subpopulation of nerve fibers and is a good approximation of the single AP shape, which is also supported by its triphasic form. In the remaining part of the manuscript we refer to it as AP. The mean amplitude of the recorded AP was slightly adjusted (correction of the direct current offset present in the recording equipment) to give a perfect zero mean. Artificial zero mean nerve cuff signals were then generated on a time interval [0,100 ms] resulting from linear superposition of 1–61 790 AP's. Superposition of more than 100 AP's resulted necessarily in overlap of AP's. For each of the resulting 61 790 signals we calculated the time-average estimate of the variance $\langle s^2 \rangle$ and of the rectified signal $\langle |s| \rangle$. The time-average estimate of the single AP variance was calculated as well: $\langle \mathrm{AP}^2 \rangle$. $\langle - \rangle$ denotes time averaging on $[L, T-L]$ interval.

C. Real Nerve Cuff Recording Processing

Nine feline sacral root S1 nerve cuff recordings (from five cats) [8] were sampled at 8 kHz (for 125 ms) during rapid bladder injections that excited bladder wall afferents, during rectal mechanoreceptor stimulation, or during the stimulation of the sacral dermatomes. Activity in the S1 nerve root increased due to increased firing frequency of different receptors. It was possible to detect the onset of bladder pressure rise caused by rapid bladder injection by maximum likelihood (maximizing cumulative sum of likelihood ratios = CUSUM algorithm) detection of change in signal variance [9].

Histograms were computed for the actual nerve cuff recording and for the artificially generated nerve cuff signals. Also, goodness-of-fit tests (Pearson's method) [6] were performed to verify the hypothesis of the Gaussian probability density function. Distributions computed from 1000 and/or 2000 samples of the artificial and actual nerve cuff signals, respectively, were tested for Gaussian probability distribution having zero mean and the variance estimated from the signal. k =18 intervals (classes) were used in the goodness-of-fit tests that covered the peak of the distribution as well as the tails. Goodness-of-fit test

$$\text{Null hypothesis: } H_0\text{: } p_1 = p_{10}; \ldots; p_k = p_{k0}.$$

The random variable c used in the test (if c is lower than the significance level of chi-squared distribution with $k-1$ degrees of freedom, the H_0 hypothesis is accepted)

$$c = \chi^2 = \sum_{i=1}^{k} \frac{(n_i - np_{i0})^2}{np_{i0}}.$$

Autocorrelation functions were computed for the actual nerve cuff recordings, the artificial nerve cuff signals, and the single AP. They were compared with respect to their amplitude and time course and may be used to explain the spectral properties of the nerve signals.

III. Results

A. Theoretical Results

Consider first time-average estimate of the variance of the nerve cuff signal [due to linearity the signal has a zero mean, since $\mathrm{AP}(t)$ has a zero mean]

$$\langle s^2(t, \boldsymbol{t_{01}}, \ldots, t_{0N}) \rangle_T = \frac{1}{T} \int \left(\sum_{i=1}^{N} \mathrm{AP}(t - t_{0i}) \right)^2 dt. \tag{3}$$

Squaring the quadratic term gives

$$\langle s^2 \rangle = \sum_{i=1}^{N} \frac{1}{T} \int \mathrm{AP}^2(t - t_{0i})\, dt + \frac{1}{T} \int \sum_{\substack{i,j \\ i \neq j}}^{N} \mathrm{AP}(t - t_{0i}) \cdot \mathrm{AP}(t - t_{0j})\, dt. \tag{4}$$

Next, the expected value $E\{\langle s^2 \rangle\}$ with respect to independent, uniformly distributed random variables $\boldsymbol{t_{0i}}$ (ensemble average) is taken resulting in cancellation of the cross terms and, thus, the second term in (4), since

$$\begin{aligned} &\int_{t_{0i}=0}^{T-L} \int_{t_{0j}=0}^{T-L} \mathrm{AP}(t - t_{0i}) \cdot \mathrm{AP}(t - t_{0j}) \left(\frac{1}{T-L} \right)^2 dt_{0i}\, dt_{0j} \\ &= \left(\int_{t_{0j}=0}^{T-L} \mathrm{AP}(t - t_{0j}) \left(\frac{1}{T-L} \right) dt_{0j} \right)^2 \\ &= 0 \text{ for } t \in [0, T-L]. \end{aligned} \tag{5}$$

Neglecting the cross-terms for $t \in [T-L, T]$ ($L \ll T$, boundary effects) and noting that the first term in (4) does not depend on random variables $\boldsymbol{t_{0i}}$ after integration by time, the final result is

$$E_{t_{01}, \ldots, t_{0N}} \{ \langle s^2 \rangle \} \approx N \cdot \langle \mathrm{AP}^2 \rangle. \tag{6}$$

Thus the expected value of the time-average estimate of the nerve cuff recording variance is proportional to the number of AP's N and to the time-average variance estimate of the single AP waveform.

The second part of our analysis concerns the probability density function of the nerve cuff signal. Fixing time at $t = t_k$ produces a random variable $\boldsymbol{s}(t_k, \boldsymbol{t_{01}}, \ldots, \boldsymbol{t_{0N}})$. It is convenient now to view each $\mathrm{AP}(t_k - \boldsymbol{t_{0i}})$ as being an independent random variable $\mathbf{AP_i}$. The random variable $\boldsymbol{s}(t_k, \boldsymbol{t_{01}}, \ldots, \boldsymbol{t_{0N}})$ is then given by a sum of identically

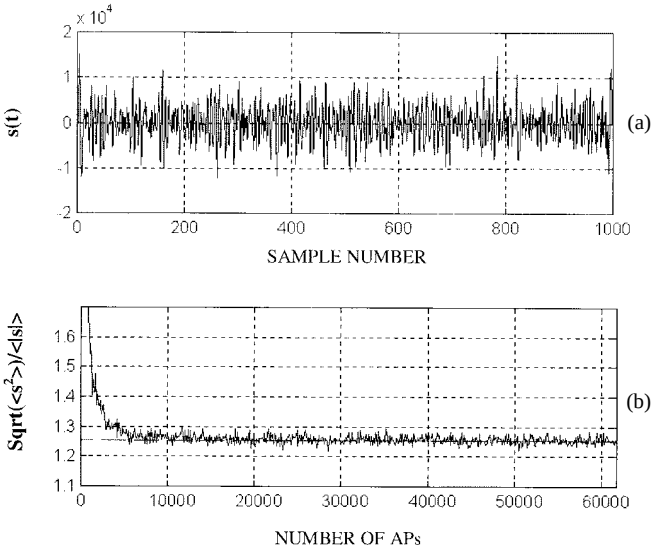

Fig. 1. In the top graph, the artificial nerve cuff signal is shown, generated by 61 790 AP's, with each AP having a duration of 1 ms. One thousand samples correspond to 100 ms. The bottom graph shows the convergence of the ratio square root($\langle s^2 \rangle$)/$\langle |s| \rangle$ for artificial nerve cuff signals toward theoretically expected value of 1.2533 (dashed line) as a function of the number of AP's.

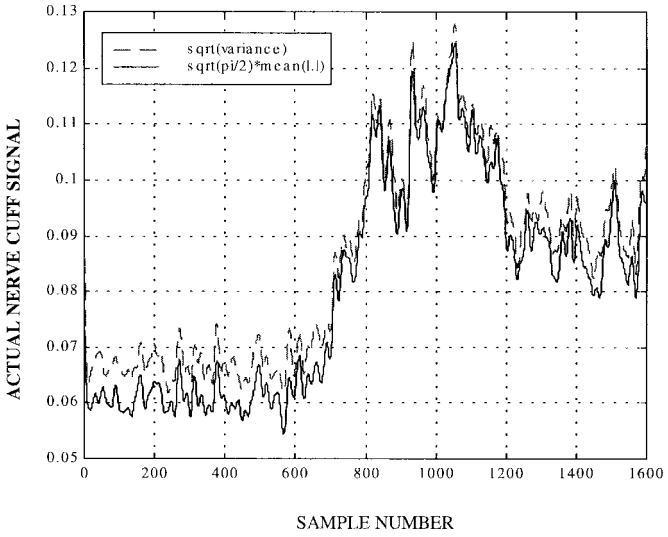

Fig. 2. A good agreement between the standard deviation of the raw actual nerve cuff signal and 1.2533 times the time-averaged rectified raw nerve cuff signal is found during the increased bladder afferent activity. This result follows from (2) and (6). The ratio is higher during the beginning of the recording, when most of the fibers were probably silent and most of the signal was, thus, electrical noise.

distributed random variables $\mathbf{AP_i}$ (since $\boldsymbol{t_{0i}}$ are identically distributed). As the number of AP's N goes to infinity, the central limit theorem applies [6] stating that the resulting probability density function will be Gaussian with mean $E\{\boldsymbol{s}\} = N * E\ \{\mathbf{AP}\} = 0$ and variance $E\{\boldsymbol{s}^2\} = N * E\ \{\mathbf{AP}^2\}$. The latter result agrees with (6). Due to the finite nonzero length of each AP, $\boldsymbol{s}(t_k, \boldsymbol{t_{01}}, \ldots, \boldsymbol{t_{0N}})$ is only correlated to $\boldsymbol{s}(t_l, \boldsymbol{t_{01}}, \ldots, \boldsymbol{t_{0N}})$ for $|t_k - t_l| < L$. Signal samples separated in time by more than L are, thus, uncorrelated and also independent. Each realization of $s(t)$ is, thus, approximately i.i.d. Gaussian signal.

The autocorrelation function of $s(t)$ is given by

$$E\left\{\left(\sum_{i=1}^{N} \mathrm{AP}(t - t_{0i})\right) \cdot \left(\sum_{j=1}^{N} \mathrm{AP}(t - t_{0j} - \tau)\right)\right\}. \quad (7)$$

Again it can be observed that the above expression reduces to $N * E\{\mathrm{AP}(t - \boldsymbol{t_{0i}})\mathrm{AP}(t - \boldsymbol{t_{0i}} - \tau)\}$. Autocorrelation of the nerve signal is, therefore, equal to N times the autocorrelation of the AP. The Wiener–Khintchine theorem, thus, implies that the power spectral densities of the nerve signal and the single AP will have the same shape, scaled by N in amplitude.

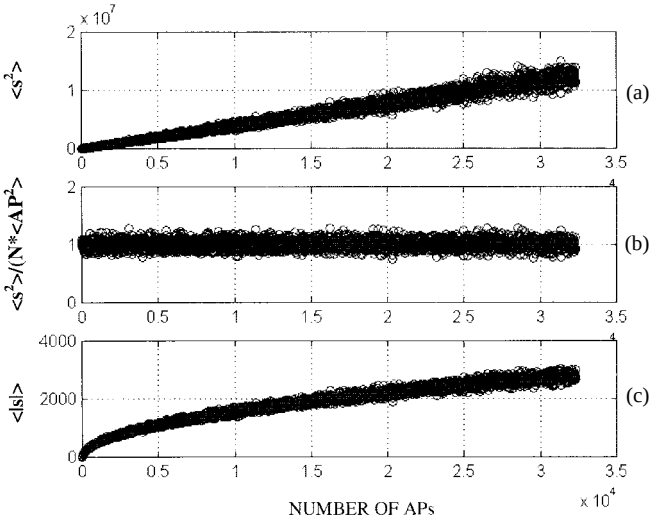

Fig. 3. (a) Variance of the artificially generated nerve cuff signal increases proportionally with the number of AP's N that generated the artificial signal, (b) shown is the exact proportionality of variance to N, the number of AP's (the expected value of the plotted ratio is one), and (c) the time-averaged, rectified artificial nerve cuff signal is proportional to the square root of N.

B. Simulations and Real Nerve Cuff Recording Results

Fig. 1 shows an artificial nerve cuff signal generated by 61 790 AP's and the left side of (2), calculated for the artificial signals generated by $N = 1$ to $N = 61\,790$ AP's. The ratio (2) assumes the values around theoretically expected value 1.2533 for signals generated by more than 5000 AP's (mean $\pm$SD $= 1.28 \pm 0.02$ calculated for signals between $N =$10 000 and $N =$60 000). Good agreement of (2) is also found for an actual nerve cuff recording (Fig. 2), when the nerve fibers are active (samples 700–1200). The ratio from (2) is higher than 1.2533 when the nerve fibers are not active (probably due to the properties of the noise present during this recording). Fig. 3(a) depicts the time-average estimate of the variance of the signal $s(t)$ depending on the number N of AP's used in generating $s(t)$. Also shown is the ratio $\langle s^2 \rangle / (N * \langle \mathrm{AP}^2 \rangle)$ which should ideally be close to 1 [Fig. 3(b)]. The time-averaged rectified signal values are shown to follow the square root of $N(\mathrm{sqrt}(N))$ relation as can be seen in Fig. 3(c). This can be explained by (2) and (6).

The actual nerve cuff recording and its histogram are shown in the top of Fig. 4 and compared to those for an artificial nerve cuff signal in the bottom. Plotted is also the ideal Gaussian probability density function of the artificial

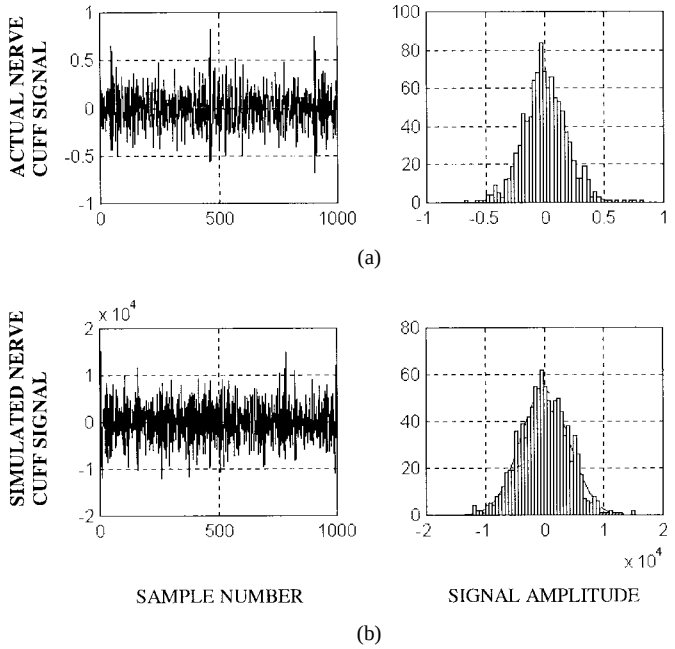

Fig. 4. Compared are the time course and the histograms of the actual nerve cuff recording (top) and the artificially generated nerve cuff signal (bottom). Both histograms are approximately bell shaped.

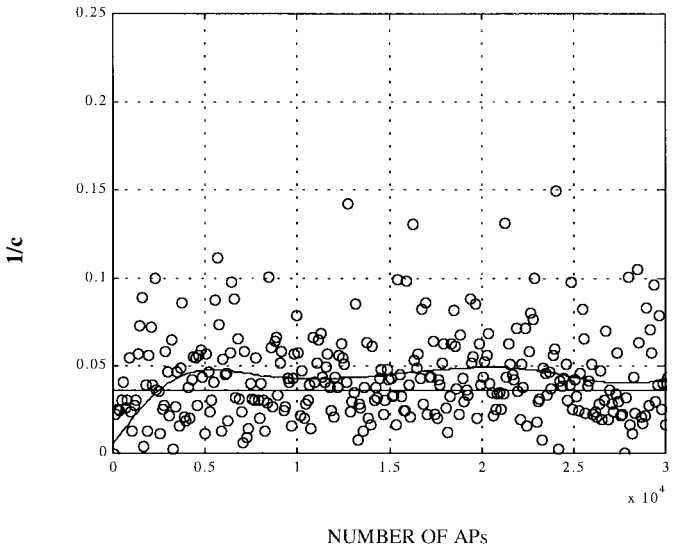

Fig. 5. Values of $1/c$ laying above the solid line at 0.036 indicate the acceptance of the Gaussian probability distribution of the artificially generated nerve cuff signal (at 0.05 significance level). First value above the solid line occurred at $N = 480$. Goodness-of-fit test (Pearson's method with 18 classes) was performed using 1000 samples of each artificial nerve cuff signal. Plotted is also the mean value of 1/c that crosses the 0.05 significance level line at about 2500 AP's.

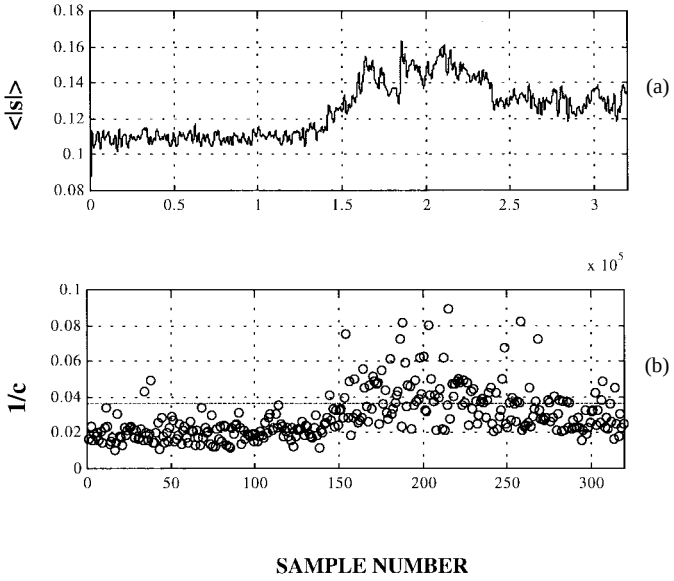

Fig. 6. Top trace (a) shows the rectified and time-averaged S1 nerve cuff signal recorded during rapid bladder distension. Bladder afferent activity increased with the increased bladder pressure. (b) Testing of the Gaussian probability distribution hypothesis for the actual nerve cuff signal shown in (a). During increased nerve activity the signal had a Gaussian distribution (values of $1/c$ above the dashed line). Each value of $1/c$ represented by a circle was calculated by goodness-of-fit test (Pearson's method) using 1000 samples of the actual nerve cuff signal.

nerve signal (dotted line). Both histograms are approximately bell-shaped. Fig. 5 depicts inverse values of the chi-square distributed random variable $\boldsymbol{c}$ used for testing the hypothesis of Gaussian probability density function for artificially generated nerve cuff signal (goodness-of-fit test). The values above the 0.05 significance level (solid line at $1/c = 1/27.6 = 0.036$) indicate the acceptance of hypothesis that the distribution is Gaussian. The significance levels of the test were 27.6, 30.2, and 33.4 for 5%, 2.5%, and 1% levels, respectively (chi-square distribution with 17 degrees of freedom). Signals generated by more than 500 AP's start having Gaussian distribution. The mean of the test variable is also plotted in the Fig. 5 and crosses the 0.05 significance level at about 2500 AP's. This means that for more than one half of artificial nerve cuff signals (64%) generated by 500–30 000 AP's the Gaussian distribution hypothesis was accepted.

A total of nine actual nerve cuff recordings was tested for Gaussian probability density function with the data originating from five cats. In cat 1, the Gaussian hypothesis was clearly accepted in both analyzed recordings, when the bladder receptors became active. Also in cat 2 (three recordings) the increased nerve firing made the signal "more" Gaussian (the Gaussian hypothesis was accepted more times and also with higher confidence intervals: the values of $1/c$ became higher). The results of the test in cats 4 and 5 are less obvious (one recording was analyzed for each cat), but some tendency to higher values of $1/c$ test variable was observed during increased nerve activity. In cat 6, the values $1/c$ increased in one recording during the activation of the receptors, but stayed more or less the same or decreased in another recording, for which we have no explanation. It needs to be said, however, that the goodness-of-fit testing of the actual nerve cuff signals was impaired due to low signal to noise ratio. There was also a background nerve activity present in the sacral root recordings when we did not excite specific receptors targeted in our study and, thus, the Gaussianity test was also testing the distributions of the background nerve activity at low signal levels. The goodness-of-fit test applied to an actual nerve cuff signal recorded during rapid bladder distension is shown in

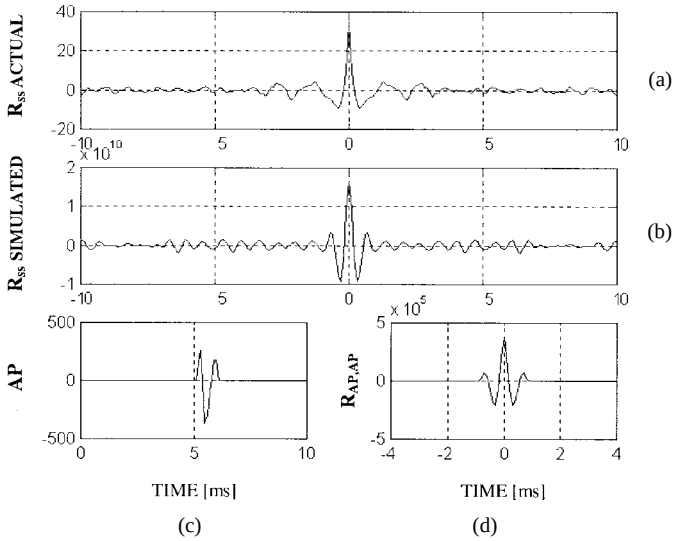

Fig. 7. Bottom left trace (c) shows the CAP recorded in the pig pelvic nerve cuff after stimulation of the sacral root S3. This AP was used for generation of the artificial nerve cuff signals. The other three graphs show the autocorrelation functions of the (a) actual nerve cuff recording, (b) simulated nerve cuff signal, and the (d) autocorrelation function of the single AP. They all approach zero after ± 1 ms as expected, since the duration of the single AP is 1 ms.

Fig. 6. Test is performed on 1000 samples throughout 320 000 samples (40's). First trace shows the rectified and time-averaged nerve cuff signal that increases when the bladder afferents increase their activity due to increase in the bladder wall tension caused by rapid injection of saline into the bladder. It can be seen that in the beginning, when the afferents are silent, the signal is not Gaussian, but acquires Gaussian probability density function when the afferents become active.

Theoretical results regarding autocorrelation functions were also in agreement with the simulated and actual nerve cuff recordings. The autocorrelation functions of an actual nerve cuff recording during bladder distension, artificial nerve cuff signal and of the single AP are shown in Fig. 7 together with the typical triphasic AP used in simulations. The triphasic form of the AP is a consequence of the filtering effect of the cuff electrode (second difference filtering) on the form of monopolarly recorded AP. Note the great similarity of the shapes of the three autocorrelation functions. They all approach zero at time-lags larger than ± 1 ms (since the duration of the AP is approximately 1 ms). The amplitude of the autocorrelation function of the artificially generated nerve cuff recording is about 45 000 times the amplitude of the autocorrelation function of the single AP. Ideally this ratio should be close to $N = 61\,790$, so it is reduced by 18.2% of the theoretically predicted value [see (7)]. The first minimum peaks are reached at 0.625, 0.30, and 0.32 ms, the first zero crossings at 1.36, 0.50, and 0.56 ms, and the first maximum peaks at 1.75, 0.68, and 0.72 ms for the actual, simulated and single AP autocorrelation functions, respectively. Thus, qualitatively, the simulated nerve cuff signal autocorrelation function and the single AP autocorrelation function are similar in the shape, and the actual nerve recording autocorrelation function is stretched out in time. The likely explanation for this is that the bladder afferents are small A-delta myelinated fibers that are slowly conducting. The recorded single AP shape was however extracted at threshold current stimulation, where bigger, faster conducting fibers were stimulated.

IV. Discussion

Although some simplifications were undertaken during the mathematical derivation of the statistics of the nerve cuff recording (assumed single AP shapes), the results obtained with computer simulations and actual nerve recording data are comparable with the theoretical results. In practice, nerve fibers with different axonal size are expected to be active at the same time. In that case, the shape of different AP's will not be the same [5], [10]. Slower conducting fibers will have AP's stretched out in time, resulting in a wider nonzero autocorrelation function and lower frequency content of the power spectral density. However, nerve cuff signal model using summation of only one distinct AP waveform was found sufficient to explain statistical properties of nerve cuff recordings. Moreover, it can easily be seen that in the case of several different AP's, the variance of the superimposed signal will be proportional to the linear combination of single AP's variances with the numbers of corresponding AP's as coefficients of the linear combination: $\mathrm{Var}(s) = N_1 * \mathrm{Var}(\mathrm{AP}_1) + N_2 * \mathrm{Var}(\mathrm{AP}_2) + \cdots + N_i * \mathrm{Var}(\mathrm{AP}_i) + \cdots$. This is true when the sources are independent, and the power, thus, adds linearly.

Specifically, we have shown that rectifying and averaging a nerve cuff signal results in a signal proportional to square root of the number of AP's, N. To yield a signal directly proportional to firing frequency or number of active nerve fibers, squaring is, thus, required. It was also shown that the same information about the number of AP's is contained in the variance of the raw nerve cuff signal. Since the signal was proven to be approximately Gaussian with zero mean, it becomes clear, that it is the variance of the signal that is really changing with varying nerve activity. The problem of signal detection can, thus, be addressed by detecting changes in variance of the raw nerve signal or, analogously, changes in mean of the rectified and time-averaged nerve signal. One way of doing this is by applying maximum likelihood detection (CUSUM algorithm) [9].

The nerve cuff signal will still have Gaussian distribution even when generated by fibers belonging to several different axonal size populations, since a sum of normal random variables is still a normal random variable. The latter result might explain difficulties of some denoising algorithms that try to differentiate between Gaussian additive noise and nerve cuff signals to separate signal and noise [11]. Furthermore, results shown in Fig. 6 actually indicate that the amplifier noise is not Gaussian (although its distribution is symmetric). Results published in [11] that show non-Gaussian nerve cuff signal distribution might have been a consequence of the EMG pickup, which is minimal or absent during recording from bladder afferents in an acute experiment.

Information on the active nerve fibers can be obtained from the autocorrelation function of the raw nerve cuff signal. The shape of the autocorrelated single AP should become evident,

allowing determination of the length of AP, and indirectly of the nerve fiber conduction velocity (using information on nerve cuff geometry). The power spectral density of a nerve signal generated by differently shaped AP's will however deviate from the shape of the signal generated by only one single AP shape. We expect the spectrum to be a weighted average of different single AP spectra. The nerve cuff signal autocorrelation function could be used to differentiate between the nerve signals and would allow classification of the most active nerve fibers.

V. Conclusions

ENG recordings made by means of whole nerve cuff electrodes have approximately i.i.d. Gaussian statistical distribution. This follows from the fact that the signal is generated by superposition of several independent, random AP's, since whole nerve contains hundreds of single axons firing with frequencies up to 1 kHz. This signal has a zero mean and variance proportional to number of AP's, N, counted in a fixed length time window. The detection of the nerve activity increases can, therefore, be addressed by detecting an increase in the raw ENG variance, or detecting an increase in the mean of the rectified and time-averaged nerve signal. The latter signal is proportional to the square root of N, and should be squared to yield a measure proportional to nerve activity (N). The autocorrelation function and, thus, the power spectral density (frequency spectrum) of the nerve cuff recording is primarily determined by the shape of the single AP, but will deviate from it in case where several different AP's are recorded in the same time window. The autocorrelation functions could allow classification of the active fibers that are making up the composed nerve cuff signal. The statistical analysis of the simulated nerve cuff signals and the actual nerve cuff recordings was found to be in accordance with the mathematical derivations presented in the manuscript.

Acknowledgment

Experimental data used in this paper were collected in collaboration with Dr. W. M. Grill at the Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH. The authors would like to thank Dr. W. M. Grill for his help during the cat experiments, Dr. J. G. Wen for the help during the pig experiments, and Dr. M. Sahin for using his preamplifiers.

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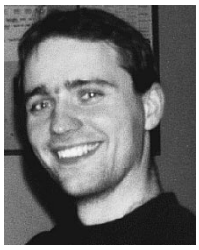

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