Quantification of depth of anesthesia by nonlinear time series analysis of brain electrical activity

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We investigate several quantifiers of the electroencephalogram (EEG) signal with respect to their ability to indicate depth of anesthesia. For 17 patients anesthetized with sevoflurane, three established measures (two spectral and one based on the bispectrum), as well as a phase space based nonlinear correlation index were computed from consecutive EEG epochs. In the absence of an independent way to determine anesthesia depth, the standard was derived from measured blood plasma concentrations of the anesthetic via a pharmacokinetic/pharmacodynamic model for the estimated effective brain concentration of sevoflurane. In most patients, the highest correlation is observed for the nonlinear correlation index D^*. In contrast to spectral measures, D^* is found to decrease monotonically with increasing (estimated) depth of anesthesia, even when a ''burst-suppression'' pattern occurs in the EEG. The findings show the potential for applications of concepts derived from the theory of nonlinear dynamics, even if little can be assumed about the process under investigation.

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I. INTRODUCTION

Several recent publications have used analysis methods derived from the theory of nonlinear dynamics to describe aspects of neuronal activity. Measures like the estimated largest Lyapunov exponent or the correlation dimension (D_2) were repeatedly applied [1,2] to quantify brain electrical activity, for example under the influence of epileptic processes, during different mental states, or in different sleep stages. Attempts to interpret the absolute numbers obtained in terms of ''system complexity,'' ''attractor dimension,'' ''chaoticity,'' or the like have met harsh and justified criticism [3]. Any such interpretation would require some narrow assumptions (stationarity, predominant low dimensional determinism, etc.) which are expected to be violated when biological time series are analyzed. On the other hand, commonly applied linear or power spectral measures are based on different, but equally narrow assumptions, including (weak) stationarity and Gaussianity. The success of these latter methods is undisputed because of the practical usefulness of the results. In this paper, we will try to take such a pragmatic attitude and compare a number of indicators of human electroencephalogram (EEG) time series with respect to their power in monitoring depth of anesthesia.

Keeping patients at a well-defined level of anesthesia is still a difficult problem in clinical practice. If anesthesia is too deep, a decompensation of the cardiovascular system is threatening. When anesthesia is too flat, the patient may wake up. Depth of anesthesia is expected to be reflected in the EEG. Some of the underlying mechanisms are known from animal studies. The EEG is generated by electrical discharges (i.e., postsynaptic potentials) of neurons located near to the surface of the brain (predominantly neurons from the neocortex) [4]. During the awake state, complex tasks can be processed by these cells. Neuronal activity changes during anesthesia as well as during ''synchronized'' sleep (including all sleep phases except for the rapid-eye-movement-sleep, in which most dreams are experienced). In the middle of the brain (i.e., in the thalamus), neuronal populations start to produce an oscillating activity that increasingly synchronizes neocortical neurons. Simultaneously, the excitability of neocortical neurons decreases so that the amount of interactions between them decreases as well. Finally, nearly all neocortical neurons fall silent. This state will not be reached during normal sleep, it is only observed during coma or deep anesthesia. A small number of thalamic oscillators can even be active during this phase. Before a continuous zero line occurs in the EEG, a so-called burst-suppression phase can appear, where volleys from these thalamic neurons account for a cyclic excitation of the silenced neocortex [5].

The described features, except for the zero line, can be seen in Fig. 1. Note the marked hysteresis: The burst suppression disappears only about 1 min after the plasma concentration of the anesthetic is reduced. The scenario may be summarized by the hypothesis that with increasing depth of anesthesia, the highly complex activities of the awake state are increasingly superimposed and replaced by more simple oscillators. Of course, such a picture amounts to a gross simplification. The full mechanism will certainly not be well described by a single parameter like ''depth of anesthesia.''

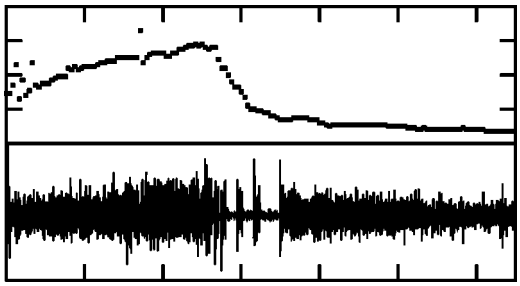

FIG. 1. EEG from a patient during anesthesia. The concentration of the anesthetic drug was increased until burst suppression first occurred (here at about 5 min) and then reduced again. The EEG is given in uncalibrated A/D units.

II. VALIDATION OF MEASURES FOR DEPTH OF ANESTHESIA

In current clinical practice, one or a few channels of EEG are routinely displayed during difficult anesthesias. Since the attending personnel has to monitor several critical parameters (blood pressure, heart rate, etc.), the vast amount of information contained in the EEG must be severely condensed in order to be useful. Only a few numbers may be monitored at a typical intervention time scale. Most pragmatically, a single number should be produced that indicates the instantaneous depth of anesthesia of the patient.

In order to derive and to validate such a measure of depth of anesthesia, the ''true'' level of anesthetic depth has to be known. One possible definition is to take the concentration of the anesthetic drug in the brain tissue as an indicator. This is reasonable if a monotonic relationship between the concentration of a single drug and the depth of anesthesia can be assumed. However, when multiple drugs are used, the drug interactions may become unpredictable. Unfortunately, even if a single drug is given, its brain concentrations cannot be measured directly in human patients. In order to circumvent this difficulty, in this study the gaseous (volatile) drug *sevoflurane* was used which can be employed as single anesthetic. In that case the concentration of the drug in the expired air can be measured, which is proportional to the blood-plasma concentration of sevoflurane. Then, by considering the brain as a hypothetical effect compartment, the equilibration of plasma concentration C_p and the concentration in the brain C_e can be modeled in a standard way by

$$\frac{dC_e}{dt} = k(C_p - C_e), \tag{1}$$

where k is the constant of equilibration that will vary from patient to patient. Since k is unknown, it has to be obtained by a fit of this pharmacokinetic model to the data. Equation (1) expresses the hysteretic response noted above to a change in the amount of sevoflurane administered.

As a further complication, the pharmacodynamic relation between the concentration in the brain as the effect compartment C_e and the neuronal effect E is not known *a priori*. A reasonable assumption is that there exists a one-to-one monotonic relationship. In that case, and if $C_e(t)$ and $E(t)$ are sampled at discrete times sufficiently far apart to assume statistical independence, this can be expressed by Spearman's rank correlation. Independence is not a reasonable assumption for consecutive values of a slowly varying quantity. Therefore, we cannot use the absolute value of Spearman's rank correlation for a formal statistical test. However, since the conditions are identical for all the methods we want to compare, significant *differences* in the correlation may be evaluated.

The aim of our analysis here is to relate the measured C_p and some estimated value $\hat{E}$ of the neuronal effect E, assuming the kinetic model, Eq. (1). Let R_i be the rank of $C_e(i)$ among all available C_e's and S_i the rank of $\hat{E}(i)$ among all the corresponding $\hat{E}$'s. An estimate for k can then be found by minimizing the sum of the squared differences of ranks:

$$\sum_{i=1}^{N} (R_i - S_i)^2. \tag{2}$$

The corresponding rank correlation coefficient [6]

$$\rho = \frac{\sum_i (R_i - \overline{R})(S_i - \overline{S})}{\sqrt{\sum_i (R_i - \overline{R})^2}\sqrt{\sum_i (S_i - \overline{S})^2}} \tag{3}$$

quantifies the success of the fit and can thus be used as a performance index for a method to estimate the neuronal effect.

For our study, 17 patients undergoing an elective surgery were anesthetized with sevoflurane. As described above, being unable to directly measure the brain concentration C_e, we measured the concentration in the breathed air at the end of expiration, which is proportional to the blood-plasma concentration C_p. The neuronal effect E is estimated for each patient by four different methods based on bipolar EEG recordings from frontal scalp regions. All EEG recordings used in this study were sampled at 256 Hz with 12 bit resolution. For the time-resolved evaluation, a window length of 30 s was used with windows taken every 5 s, that is, with 83% overlap. The total observation period for each patient varied between 13 and 55 min, median 34 min.

III. EEG BASED MEASURES OF ANESTHESIA DEPTH

In this study, we have compared four methods to derive an indicator for the depth of anesthesia from EEG data. Two of these measures are based on the power spectrum, one additionally takes the bispectrum into account, combined with a special feature detection scheme. The fourth is a nonlinear correlation index based on phase-space reconstruction and correlation sums. Like in any other problem of EEG characterization, none of the used methods is derived from first principles nor can any one be fully justified on physiological grounds. Rather, they aim at a useful reduction of the vast amount of information in an EEG trace to one or a few numbers that may be monitored with justifiable effort.

A. Power spectral measures

Apart from visual inspection, the most common method to analyze and quantify time series data in clinical medicine—often the only viable one with the given data quality—is the frequency power spectrum, usually computed using the Fourier transform. Spectral estimation in itself provides only a moderate reduction of information, except in the case that dominant oscillators can be identified by sharp spectral lines and overtones. The art of spectral analysis is to define key parameters that turn a power spectrum into a number, or at most a few essential quantities. For line spectra, the positions and widths of the resonances are obvious candidates. For broadband spectra like the EEG, one may consider the spectral content in certain frequency bands, characteristic frequencies, etc.

Here we use two ''classical'' spectral parameters [7–9] that have been previously applied for this purpose. The *spec-*

tral edge frequency 95% [10] indicates the maximal relevant frequencies while the *median frequency* [11] gives a rough indicator over the overall typical frequency of the recording. The physiological motivation lies in the expectation that at deeper levels of anesthesia, high-frequency components of the surface EEG should be suppressed due to the entrainment by slow oscillations in more central regions of the brain. Therefore, both indices are expected to decrease with an increasing depth of anesthesia.

Both measures are based on the time windowed Fourier transform (using 5% cosine tapering of window edges) $H(f)=\Sigma_{t=0}^{N-1}h(t)\exp(2\pi itf/N)$ of the digitally sampled EEG time series $h(t)$. Inspecting the spectral band between $f_{\mathrm{low}}=0.25$ Hz and $f_{\mathrm{high}}=30$ Hz, the accumulated periodogram

$$P(f)=\sum_{i=f_{low}}^{f}|H(i)|^2 \tag{4}$$

is used to determine the two spectral parameters, the *spectral edge frequency 95%*, here denoted by f_{se95}, and the *median frequency* f_{median}. The parameter f_{se95} is defined as the frequency at which $P(f_{\mathrm{se95}})=0.95\,P(f_{\mathrm{high}})$ and the median frequency f_{median} as the frequency at which $P(f_{\mathrm{median}})=0.5\,P(f_{\mathrm{high}})$.

B. Bispectral index

A popular parameter in EEG instrumentation for anesthesia is represented by the *bispectral index* (*bis*) [12]. This composite parameter uses multiple measures of the EEG power spectrum and bispectrum as well as burst-suppression analysis and has been optimized to predict the degree of sedation. Unlike all other EEG parameters, it has been validated in large studies as a measure of sedation in anesthesia [13]. Unfortunately, the precise algorithm is proprietary and has not yet been published. The bispectrum is one possible natural generalization of the Fourier power spectrum to nonlinear signals. While the ordinary spectrum may be defined as the Fourier transform of the two-point autocovariance function $\langle x(t)x(t-\tau)\rangle$ of a signal $x(t)$, the bispectrum is obtained by a two-dimensional Fourier transform of the three-point autocovariance function $\langle x(t)x(t-\tau_1)x(t-\tau_2)\rangle$. The way the bispectral index condenses this two-variate function into a single number seems to have been established heuristically. At least no physiological motivation is given in the literature. In the absence of a published definition, we use the values of the bispectral index as computed by the *Aspect 1000* EEG monitor and record it every 5 s.

The reported relative success [13] of the bispectral index suggests that properties of the EEG beyond the power spectrum are important for distinguishing of different states of anesthesia. We do not want to enter into a discussion here of what nature the extra structure is. It is very difficult to disentangle the effects of nonlinearity and nonstationarity, and, if nonlinearity is found, to what extent it is of dynamical nature or if it merely reflects the complicated transduction properties of the intervening tissue. From a physiological point of view, the situation is rather involved. The individual neurons clearly show nonlinear behavior in their action potentials, but the law of large numbers suggests that this structure might be averaged out in surface EEG traces. Nonstationarity is very prominent in anesthesia, in particular in the burst suppression phase, where episodes of low amplitude activity are interrupted by short outbreaks of large amplitude waves. Spectral indicators are known to give spurious values in the presence of burst suppression. Therefore, the bispectral index algorithm contains a pattern recognition scheme to detect burst suppression, which is then treated separately.

C. Nonlinear correlation index *D**

Early claims of low dimensional strange attractors in brain signals have been identified as spurious due to the lack of certain precautions when using nonlinear analysis tools. (See [3,14] for further discussion and references.) This does not exclude that tools and methodologies derived in the context of dynamical systems, or chaos theory, may be still be useful when employed with care. In particular, interpretations in terms of fractality, chaoticity, complexity, and the like, have to be attempted with utmost discretion.

In that spirit, we have adapted a prescription for an overall index of (nonlinear) coherence that has been found powerful for anticipating epileptic seizures from implanted electrode recordings [15] as well as in epilepsy models on a cellular level [16]. This index, which we will call D^* contains many ingredients familiar from the Grassberger-Procaccia algorithm for the correlation dimension [17,18], whence the D. The * is there to remind us that there are important differences that preclude an interpretation in terms of fractal dimensions, number of degrees of freedom, etc.

Starting form a scalar time series $s_n, n=1,\ldots,N$, we first form delay embedding vectors as usual: $\mathbf{s}_n=(s_{n-(m-1)\tau},\ldots,s_{n-\tau},s_n)$. The correlation sum $C_m(r)$ is then defined as usual by

$$C_m(r)=\alpha\sum_{i=1}^{N}\sum_{j=1}^{i-\Delta n}\Theta(r-\|\mathbf{s}_i-\mathbf{s}_j\|), \tag{5}$$

where Θ is the step function and $\alpha=2/(N-\Delta n)(N-\Delta n-1)$ is a normalization constant. For the estimation of the correlation dimension, one would take Δn large to exclude temporal correlation and study the slope of a double logarithmic plot of $C_m(r)$ versus r and look for a *scaling region*, that is, a range of values of r where

$$C_m'(r)=\frac{d\log(C_m(r))}{d\log(r)} \tag{6}$$

is constant. For high enough embedding dimension m, that constant would be an estimator of the correlation dimension D_2. There is ample literature on using the correlation integral for dimension estimation [14].

Except for specific pathologies, we do not expect this procedure to arrive at a reasonable, finite value for D_2 when applied to the EEG. Since we cannot hope to estimate a proper dimension in the first place, there is no particular reason to concentrate on geometrical correlations only, or to aim at a proper phase space embedding. In principle, we could instead optimize parameters for the specific purpose at hand. However, a total of 17 patients is too small a population to be split into a training set and a test set and we are not

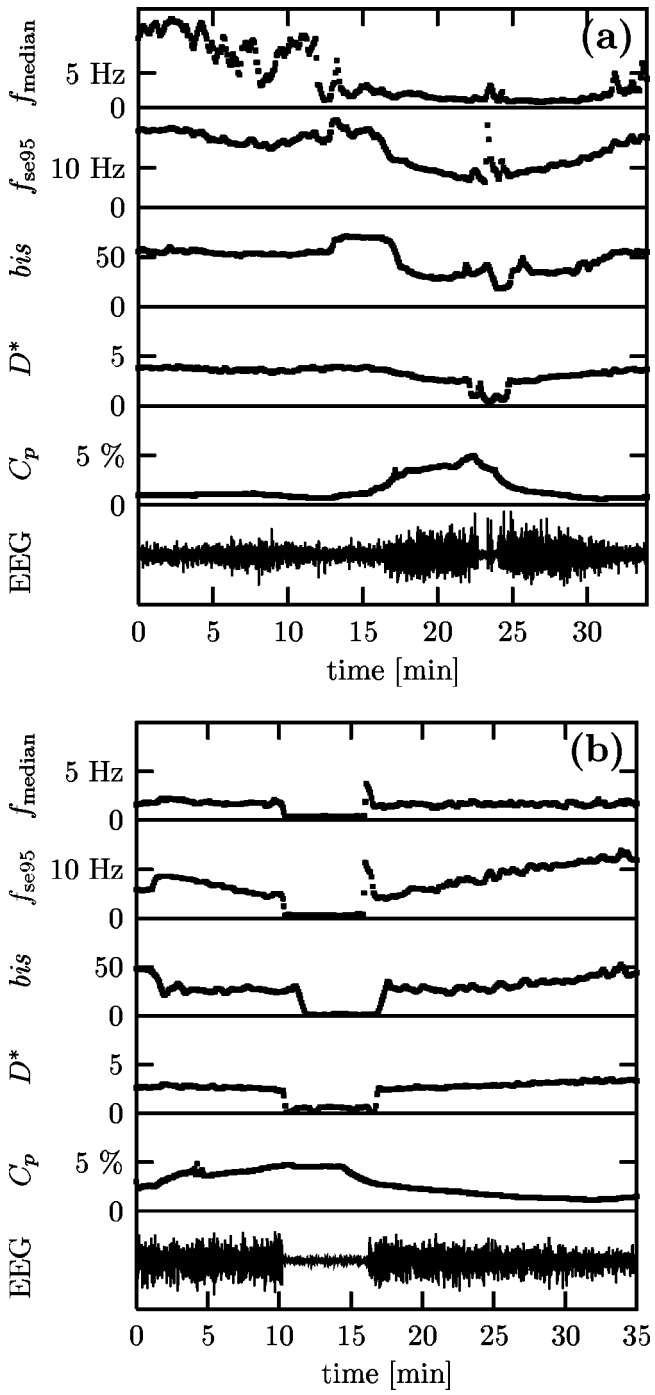

FIG. 2. Time course of two representative cases. The lowest trace shows the EEG and the second lowest the plasma concentration of the anesthetic estimated by measuring the concentration of the exhaled air. Depth of anesthesia is estimated every 5 s by four different methods. The two topmost curves denote spectral parameters, the *median frequency* f_{median} and the *spectral edge frequency 95%*, f_{se95}. The third curve shows the *bispectral index* (*bis*) as issued by the commercial monitoring equipment. The fourth curve gives the nonlinear correlation index D^*. See text for discussion.

interested in in-sample results that may be due to overfitting. Therefore, we copy the parameter settings and operational procedures from previous studies on epilepsy prediction [15] without further optimization. Using unit delay, a range of embedding dimensions $m=10,\ldots,25$ was studied and only immediate temporal neighbors with $i-j<\Delta n=10$ were excluded. Each segment of 30 s was digitally band-pass filtered (0.25–30 Hz) before computing $C_m(r)$. The operational procedure of determining a ''plateau'' value D^* of $C_m'(r)$ is also described in Ref. [15]. It is worth noting that this automatic procedure is designed to exclude both, large amplitude artifacts (large r) and small amplitude fluctuations (small r). Some conjecture on the reasons for the success of this procedure will be offered in the discussion section below.

TABLE I. Results of the fit for the relaxation parameter k.

	Median	25% quartile	75% quartile
f_{median}	0.15	0.08	1.00
f_{se95}	0.26	0.16	0.56
bis	0.34	0.22	0.44
D^*	0.24	0.18	0.41

IV. CLINICAL RESULTS

In all 17 patients the following protocol was carried out. The concentration of sevoflurane was at first slowly increased. As soon as a burst suppression pattern or even a zero line occurred in the EEG, Sevoflurane concentration was decreased again. Two typical examples of corresponding EEG time series and estimated measures of anesthesia depth are shown in Fig. 2. In case B, immediately a zero line occurs in the EEG rather than a burst suppression pattern. It is important to remember that the actual neuronal anesthetic effect is not simply proportional to the plasma concentration C_p shown in Fig. 2 but follows hysteretically through the relaxation phenomenon we modeled by Eq. (1). Generally speaking, all four measures studied are expected to show a negative correlation with the depth of anesthesia.

In both cases, a slight decline of D^*, but a small increase of *bis* precedes the burst suppression (respectively zero line) phase. The reaction of *bis* on these abrupt changes of EEG patterns is delayed. Depending on frequency characteristics of the background noise, spectral measures either decrease (**A**) or increase (**B**) during phases with a zero-line EEG. For a quantitative evaluation, we need to estimate the effective brain concentration C_e of sevoflurane. For this purpose, we assume the pharmacokinetic model given by Eq. (1) and determine an equilibration-constant k individually for each case by minimizing the sum of the squared differences of ranks between C_e and E, cf. Eq. (2). The values for k that were found [19] are summarized in Table I.

Compared to the variation from patient to patient, there were no dramatic differences among the results for the different measures of anesthesia. It is important to notice that the fit for k is only important in order to establish a mono-

TABLE II. Spearman's rank correlation ρ for the best fit.

	Median	25% quartile	75% quartile
f_{median}	-0.33	-0.06	-0.59
f_{se95}	-0.54	-0.27	-0.80
bis	-0.82	-0.60	-0.91
D^*	-0.90	-0.81	-0.94

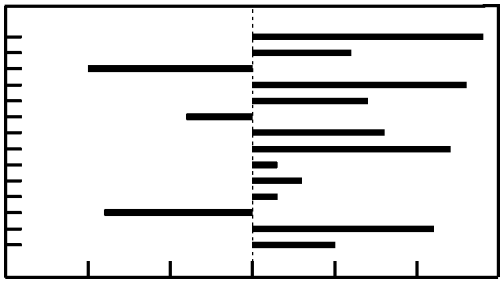

FIG. 3. Signed ranks of the differences between the correlations for D^* and *bis*. A bar to the right means that D^* correlates more strongly for that patient.

tonic relationship between an EEG measure and assumed depth of anesthesia. The parameter k describes the time course of the equilibration of anesthetic concentration between blood plasma (assumed to be equal to the concentration in the air at the end of expiration) and a hypothetical effect compartment (i.e., the brain or parts of it). It will be influenced by factors like brain perfusion, patients' age, amount of body fat, etc. However, since the value of k is no longer needed once a monotonic relationship is assured, these influencing factors need not be under close control for this approach.

Based on the optimal values for k, for each case Spearman's rank correlation coefficient ρ was computed [cf. Eq. (3)]. Table II shows that the highest correlation coefficients

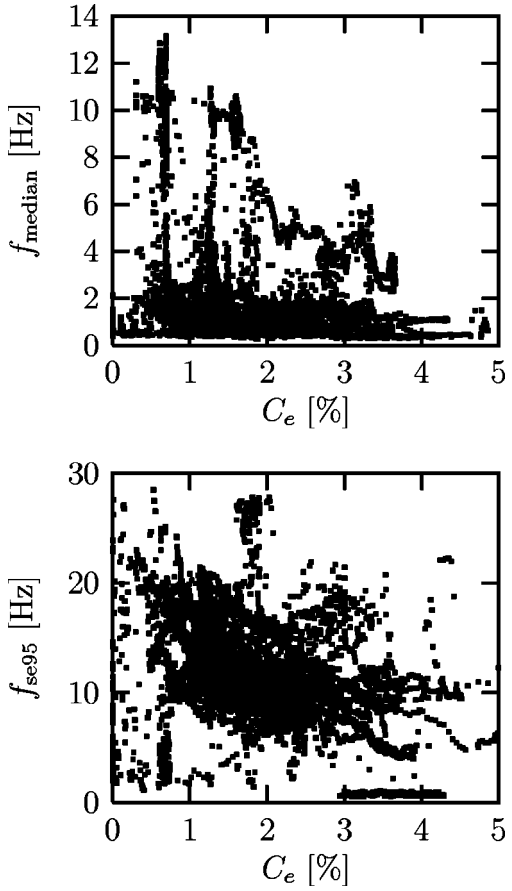

FIG. 4. Cumulative plots of the correlation with estimated anesthesia depth of the two spectral indicators f_{median} and f_{se95}, comprising all considered cases.

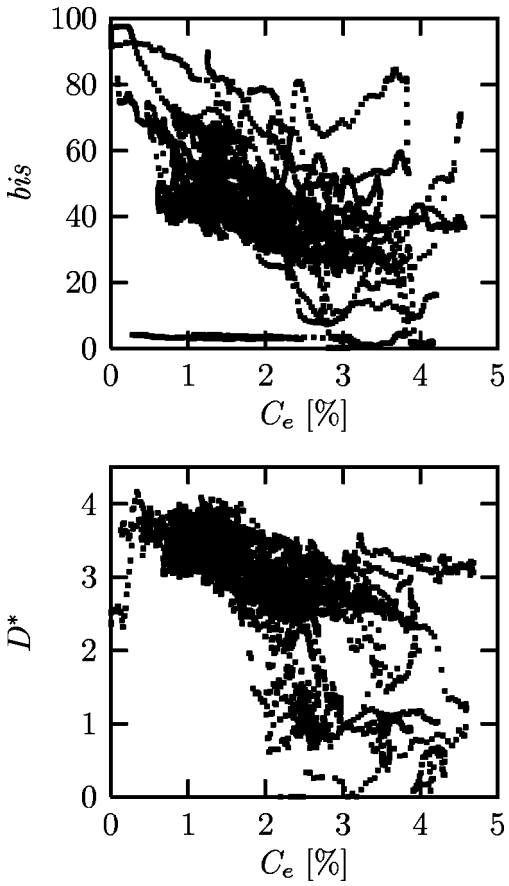

FIG. 5. Cumulative plots of the correlation with estimated anesthesia depth of the two nonlinear indicators, *bis* and D^*, comprising all considered cases.

were achieved for D^*. In order to assess the statistical significance of this finding, we have performed a nonparametric test for the hypothesis that D^* performs better than *bis*. Since the populations of values where obtained on the same patients, we evaluated the Wilcoxon matched-pairs signed-rank test (see Fig. 3) and found that the correlation is higher for D^* with $p<0.05$.

For clinical applicability, it is not sufficient to have a good correlation for each patient individually. Rather, a monotonic relationship has to hold across patients. In order to illustrate the relevance of the relation between the brain concentration of sevoflurane C_e and its estimated EEG effect E for the whole group of patients, for each investigated EEG measure a scatterplot of C_e against E, including results from all patients, is shown in Figs. 4 and 5. The corresponding rank correlation coefficients ρ are -0.06 for f_{median}, -0.33 for f_{se95}, -0.63 for *bis*, and -0.72 for D^*. Due to the serial correlations within each trial, we do not attempt a formal test of the hypothesis that a (negative) correlation exists. Visual inspection as well as the value for ρ suggests that f_{median} is essentially useless as an indicator of depth of anesthesia in the investigated group of patients. Also for the other spectral measure, f_{se95}, the correlation is rather unreliable. It is conceivable that in a study that excludes burst-suppression EEG or with additional preprocessing (e.g., by introducing a burst-suppression detector) the situation may be more favorable. Both *bis* and D^* show a certain trend to decrease with increasing depth of anesthesia. Of all the stud-

ied measures, we find that D^* comes closest to an overall monotonic relation to the depth of anesthesia.

V. DISCUSSION

In a relatively small but focused clinical study, we have compared four different methods to quantify depth of anesthesia by numerical analysis of EEG tracings. All four methods were defined outside the study whence the results can be considered to be out-of-sample. We have used the available data to answer the question which of the four measures comes closest to a monotonic relationship to the level of sedation. While for both of the two nonlinear measures, *bis* and D^*, such a relationship seems to exist, the correlation is strongest for D^*, despite the fact that *bis* had been specifically designed for this purpose in previous work.

With the limited data base available, any interpretation of the findings remains speculation. The success of D^* in previous studies on the anticipation of epileptic seizures has been discussed in Ref. [20], where it was pointed out that the connection with the epileptic alterations is lost if the temporal correlations are fully excluded from the correlation sum, as one would have to do for a dimension estimation [14]. It can be suggested that geometrical correlations are not essential but the ability to select structures—temporal or geometric—by amplitude, or length scale in phase space, makes the correlation sum superior to other nonlinear statistics.

In earlier studies, D^* has been found helpful for the anticipation of epileptic seizures [15] from intracranial EEG recordings. It has also been shown [16] that even on a cellular level D^* could quantify the complexity of the synaptic input of a single neuron when interictal epileptiform activity was induced in brain slices. The degree of autonomous activity, and hence the number of degrees of freedom of a neuronal network, is thought to decrease during the development of epileptiform activity. Indeed, a reduction of D^* extracted from intracellular recordings of single neurons was observed prior to visually detectable alterations [16].

In the common scenario of anesthesia, the number of degrees of freedom of human brain activity is lowered—as compared to the awake state—when nearly all neocortical neurons fall silent and only a central (thalamic) oscillator is able to evoke a cyclic excitation of the silenced neocortex [5]. However, the number of degrees of freedom may still be huge and is probably not accessible from an EEG time series [21]. It is even the more remarkable that D^* correctly ranks the qualitatively different EEG pattern of burst suppression as corresponding to the deepest level of anesthesia. At the onset of burst suppression, the EEG signature changes discontinuously with the estimated drug concentration, whence the relatively sharp transition in D^* between the preceding deep sleep phases and burst suppression in Fig. 5. Still, from a biological point of view it remains unclear which electrophysiological properties contribute to the monotonic decline of D^* under anesthesia—or epileptic activity.

In summary, extraction of D^* seems to be able to improve the quantification of depth of anesthesia from brain electrical activity, at least when sevoflurane is used as anesthetic drug. For clinical applicability, other anesthetics have to be investigated. The size of this study is too small to admit any optimization of the algorithm. It is conceivable, however, that the clinical reliability can be enhanced, and the computational burden relieved, by a more thorough understanding of which structures are really picked up by the algorithm.

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[19] For each of the four measures, there was one case where the fit went unstable and k could not be determined. This was most probably caused by artifacts remaining in the EEG signal. Somewhat surprisingly, though, for each of the nonlinear measures D^* and *bis*, a different patient caused the trouble, and still another one was problematic for the spectral methods.

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