Stochastic Qualifiers of Epileptic Brain Dynamics

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We evaluate the capability of reconstructing Fokker-Planck equations for an improved characterization of electroencephalographic (EEG) recordings from epilepsy patients. We derive stochastic qualifiers of brain dynamics that are based on specific characteristics of the Kramers-Moyal coefficients estimated from the EEG. Analyzing long-lasting multichannel EEG recordings from eight patients suffering from focal epilepsies we show that particularly the stochastic part of the dynamics can yield valuable information for diagnostic purposes.

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The dynamics of many natural and man-made complex systems exhibits deterministic and stochastic features. In situations where the underlying equations of motion are not known, a detailed quantitative description can nevertheless be achieved by applying time series analysis techniques to experimentally acquired observables. When the dynamics involves only a few degrees of freedom the framework of nonlinear time series analysis [1,2] provides quite powerful tools to characterize complex behavior, which allows one to estimate the underlying equations of motion from time series data. Over the past decades analyses of electroencephalographic (EEG) time series have provided valuable insight into the complex spatiotemporal dynamics of physiological and pathophysiological brain functions [3]. In epileptology, particularly nonlinear approaches were shown to allow an improved understanding of intermittent dysfunctioning of the brain between epileptic seizures and to provide potentially useful diagnostic information [4]. Moreover, these techniques provided first evidence for the existence of seizure precursors whose unequivocal detection might lead to the development of seizure prediction and prevention techniques [5]. Despite the many promising findings there are a number of problems for which there are currently no satisfactory solutions. This can be attributed to the fact that in many cases crucial aspects of pathological brain dynamics must be regarded as stochastic (high-dimensional) and thus, may not be captured when applying time series analysis techniques that preferentially focus on the low-dimensional deterministic part of the dynamics.

Dissipative dynamical systems under the influence of noise can often be successfully modeled by a Fokker-Planck or, equivalently, an associated Langevin equation [6,7], which reads $\dot{x} = D^{(1)}(x(t)) + \sqrt{D^{(2)}(x(t))}\Gamma(t)$ in the one-dimensional case. $x(t)$ denotes the state of the system and $\Gamma(t)$ is a Gaussian white noise process which is assumed to be uncorrelated, $\langle\Gamma(t)\Gamma(t')\rangle = \delta(t - t')$, with vanishing mean, $\langle\Gamma(t)\rangle = 0$. The drift coefficient $D^{(1)}$ describes the deterministic part of the dynamics and the diffusion coefficient $D^{(2)}$ determines the strength of the driving noise force. If $D^{(2)}$ depends on the state x the stochastic part is referred to as multiplicative dynamical noise, otherwise as additive dynamical noise. The Fokker-Planck equation is a special case of a more general evolution equation for continuous Markov processes, namely, the Kramers-Moyal expansion, and the coefficients $D^{(n)}$ can be defined in a statistical sense using the conditional moments of the stochastic variable $X(t)$ [8]:

$$D^{(n)}(x, t) = \frac{1}{n!}\lim_{\tau\to 0}\frac{1}{\tau}\langle[X(t + \tau) - X(t)]^n\rangle|_{X(t)=x}. \quad (1)$$

In Refs. [9–11] an analysis technique has been introduced that allows one to estimate drift and diffusion coefficients from time series data by evaluating the conditional moments in Eq. (1) for finite time steps τ and then extrapolate to $\tau = 0$. This technique has been successfully applied in a variety of disciplines ranging from physics [12–18] to the biomedical domain [19–21].

In this Letter we show that, by using this approach, an improved characterization of pathological brain dynamics can be achieved by explicitly taking into account stochastic parts of the dynamics. We retrospectively analyzed multichannel (20–60 recording sites), multiday (5–12 days) EEG recordings from eight patients with pharmacoresistant focal epilepsy who underwent evaluation for resective therapy. EEG data were recorded from the cortex and from within relevant structures of the brain, hence with a high signal-to-noise ratio. Signals were sampled at 200 Hz using a 16 bit analog-to-digital converter and filtered within a frequency band of 0.53 to 85 Hz. After surgery all patients achieved complete seizure control so the brain structure responsible for seizure generation (epileptic focus) can be assumed to be contained within the resected brain volume.

The method proposed in Refs. [9–11] requires the brain dynamics to be Markovian (a process without memory), which we checked by evaluating the Chapman-

Kolmogorov equation for the conditional probabilities $p(x(t+2\tau)|x(t))$ [8]:

$$p(x(t+2\tau)|x(t)) = \int dx(t+\tau)p(x(t+2\tau)|x(t+\tau))p(x(t+\tau)|x(t)). \quad (2)$$

We analyzed exemplary EEG time series recorded from within the epileptic focus and from a distant brain region during the seizure-free interval of one patient. For epoch lengths ranging from about 2 to 8 min we observed that Eq. (2) is approximately fulfilled for a minimum possible time shift $\tau = 1$ (in units of the sampling interval) [22]. In Fig. 1 we show typical examples of drift and diffusion coefficients estimated from EEG time series. Both coefficients can be well approximated by low order polynomials. As expected for this one-dimensional model $D^{(1)}$ indicates an overall linear damping behavior. For EEG time series recorded from within the epileptic focus we observed small nonlinearities toward higher amplitude values, which is in line with findings from studies using nonlinear time series analysis techniques [4]. The behavior of $D^{(2)}$ indicates a multiplicative influence of the noise. To test whether the deviation from an additive behavior (i.e., $D^{(2)} = \text{const.}$) was caused by the finiteness of the time shift τ [23] we followed Refs. [24,25] and considered a Taylor expansion of the second conditional moment. Using the estimated values of $D^{(1)}$ and different constant diffusion coefficients we observed that the influence of higher order terms in τ cannot explain the multiplicativity of the estimated second coefficients.

We also estimated the fourth-order coefficient $D^{(4)}$, which allows one to determine whether the driving noise process $\Gamma(t)$ exhibits deviations from a Gaussian distribution [26]. Only if $D^{(4)}$ vanishes, $\Gamma(t)$ is Gaussian and the probability density function (PDF) of the process under consideration evolves according to a Fokker-Planck equation [27]. For the EEG recorded from a distant brain region

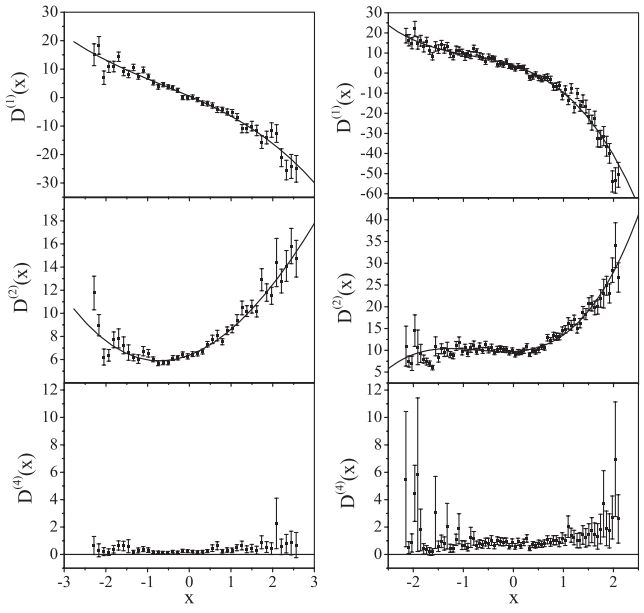

FIG. 1. Estimated coefficients $D^{(1)}$, $D^{(2)}$, and $D^{(4)}$ for exemplary EEG time series (left: from a distant brain region; right: from within the epileptic focus). Shown are estimates for time series consisting of 100 000 data points (squares) as well as fits with low order polynomials (black lines). Error bars indicate the statistical error of the estimation of the averages according to Eq. (1) for each value of x.

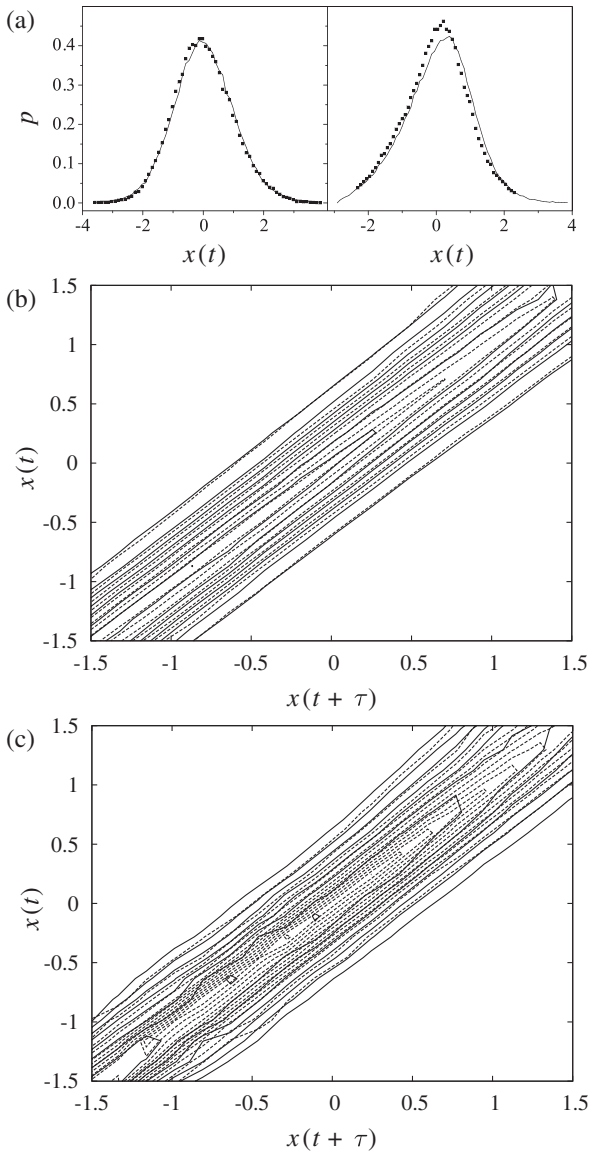

FIG. 2. Comparison of the stationary PDF's (a) and contour plots of conditional PDF's for $\tau = 1$ (b) and (c) for the EEG time series [squares in (a), dashed lines in (b) and (c)] and time series generated by integrating the associated Langevin equations (straight lines). (a) left plot and (b): from a distant brain region; (a) right plot and (c): from within the epileptic focus. Contour plots were generated using an increment between contour lines of 0.02 in (b) and 0.012 in (c).

$D^{(4)}$ took on values slightly above zero but the magnitude of this coefficient was less than one-twentieth in comparison to the second coefficient $D^{(2)}$. In contrast, for the EEG recorded from within the epileptic focus $D^{(4)}$ took on values clearly above zero. These findings indicate that a description of pathological brain dynamics by a one-dimensional Fokker-Planck model may be inadequate. This is further corroborated by our results obtained from integrating the Langevin equation [29,30] using the estimated functions $D^{(1)}$ and $D^{(2)}$ for both EEG time series (Fig. 2). While both the stationary and the conditional PDF's of the integrated model and of the EEG time series coincided quite well for the recording from a distant brain region, we observed more pronounced deviations for the recording from within the epileptic focus.

These findings clearly indicate that specific characteristics of the estimated drift and diffusion coefficients allow one to differentiate between physiological and pathophysiological activities. For this purpose we derived different quantities from the estimated coefficients that serve as *stochastic qualifiers* of epileptic brain dynamics [22]. As an example, we here consider the range covered by the values of the estimated coefficients $R_{1,2} := |\max(D^{(1,2)}(x)) - \min(D^{(1,2)}(x))|$. We here only took into account values of $D^{(1,2)}$ for which at least 100 data points were available for the estimation procedure. For the multichannel, multiday EEG recordings from all patients we performed a time resolved estimation of $R_{1,2}$ using a moving-window technique. Data windows were of size $N = 50\,000$ data points, and windows overlapped by 50%. This choice represents a compromise between sufficient statistics for a reliable estimation of $D^{(1,2)}$ and temporal resolution, which might be of interest for further EEG analyses. We stress that the determination of $R_{1,2}$ was done fully automatically and without human interference.

In Fig. 3(a) we show a typical spatiotemporal distribution of R_2 calculated for a multichannel EEG (52 contacts) recorded during the seizure-free interval from a patient with an epileptic focus located in the right hemisphere. When comparing findings from the left and right brain hemisphere we observed highest values of R_2 confined to regions close to or within the epileptic focus. We thus expected that pathophysiological activities are reflected by increased values of our measures.

Since these values showed only little variance over time we calculated, for each contact, their temporal average, ($\langle R_{1,2}\rangle_t$), and eventually averaged over all contacts c from each hemisphere ($\tilde{R}_{1,2} := \langle\langle R_{1,2}\rangle_t\rangle_c$). This allowed us to further condense the information contained in the spatiotemporal distribution of our stochastic qualifiers and to investigate retrospectively whether they can provide diagnostically relevant information. In the following we refer to the brain hemisphere containing the epileptogenic focus (determined by the presurgical workup and by the postoperative complete seizure control) as the *focal side*, whereas the opposite hemisphere is denoted as the *nonfocal side*. In six out of eight patients $\tilde{R}_1$ was higher on the

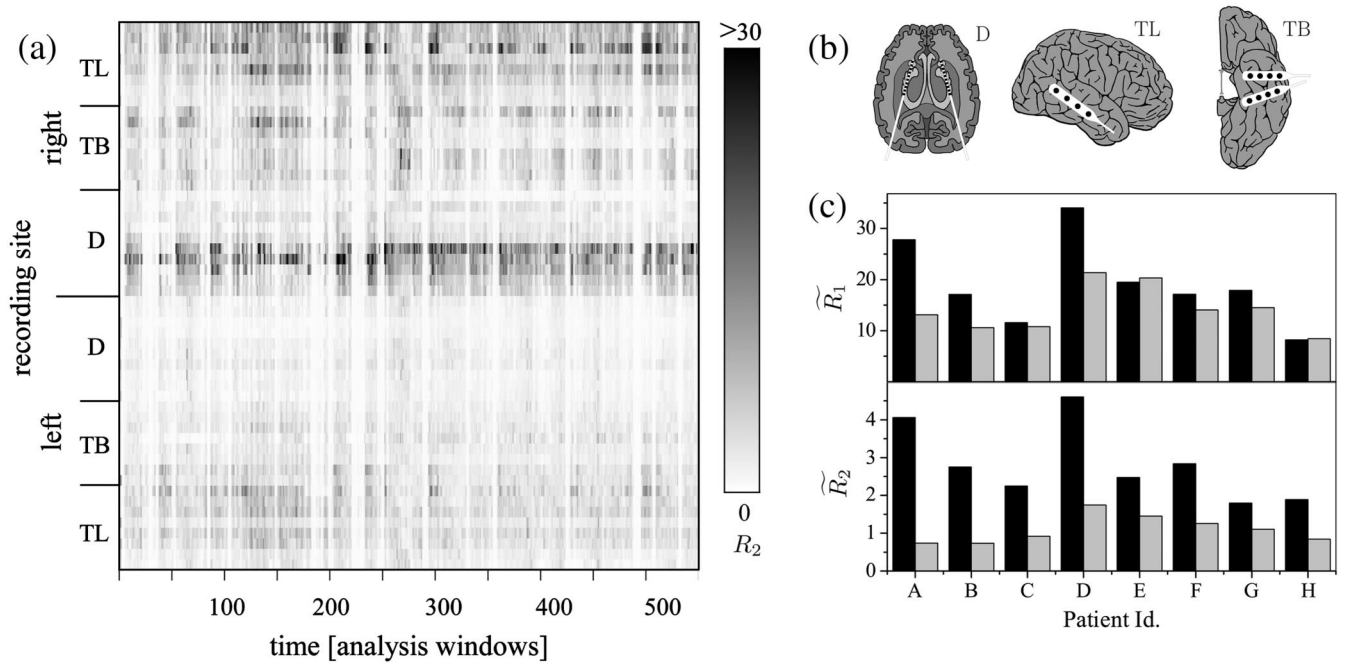

FIG. 3. (a) Time resolved estimates of R_2 calculated from a multichannel EEG recording (approximately 19 h) of a patient suffering from a right-sided focal epilepsy (patient F). (b) Implantation scheme of intracranial electrodes: hippocampal depth electrodes (10 contacts each, D), lateral (4–16 contacts, TL), and basal (4 contacts each, TB) strip electrodes. (c) Spatiotemporal means of R_1 and R_2 for all investigated patients. Black bars denote values from the focal and gray bars from the nonfocal hemisphere.

focal side. Interestingly, we observed that $\tilde{R}_2$ allowed correct identification of the focal side in *all* patients [Fig. 3(c)].

To conclude, we have investigated the applicability of a time series analysis method that is based on the reconstruction of a Fokker-Planck equation from empirical data for an improved characterization of epileptic brain dynamics. For this purpose we studied long-lasting, multichannel EEG time series that covered physiological and pathophysiological activities from the seizure-free interval of eight patients suffering from focal epilepsies. Despite limitations that can be attributed to the fact that EEG time series may not entirely meet the prerequisites of the underlying theoretical framework, a one-dimensional Fokker-Planck model appeared to be appropriate for a description of physiological activities. It may not be possible, however, to capture all aspects of pathophysiological activities in such a model. Nevertheless, we were able to derive stochastic qualifiers that allowed a more comprehensive characterization of the epileptic process particularly when focusing on the stochastic part of the dynamics. Thus, even in cases where the dynamics is not generated by a Langevin process but by a more complex process for which the Markovian property is not fulfilled in a strict sense, drift and diffusion coefficients appear to be quite useful characterizing quantities [31]. We expect that our approach along with further improvements can yield valuable information for diagnostic purposes and can advance our understanding of the complicated dynamical system epileptic brain.

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