Dynamics of Epileptic Phenomena Determined From Statistics of Ictal Transitions

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***Abstract*—In this paper, we investigate the dynamical scenarios of transitions between normal and paroxysmal state in epilepsy. We assume that some epileptic neural network are bistable i.e., they feature two operational states, ictal and interictal that co-exist. The transitions between these two states may occur according to a Poisson process, a random walk process or as a result of deterministic time—dependent mechanisms. We analyze data from animal models of absence epilepsy, human epilepsies and *in vitro* models. The distributions of durations of ictal and interictal epochs are fitted with a gamma distribution. On the basis of qualitative features of the fits, we identify the dynamical processes that may have generated the underlying data. The analysis showed that the following hold. 1) The dynamics of ictal epochs differ from those of interictal states. 2) Seizure initiation can be accounted for by a random walk process while seizure termination is often mediated by deterministic mechanisms. 3) In certain cases, the transitions between ictal and interictal states can be modeled by a Poisson process operating in a bistable network. These results imply that exact prediction of seizure occurrence is not possible but termination of an ictal state by appropriate counter stimulation might be feasible.**

***Index Terms*—Bistability, duration distribution, epilepsy.**

I. Introduction

EPILEPSY is considered a dynamic disease [1]. Such diseases are characterized by qualitative changes from normal behavior to abnormal dynamics of some variables [2]. Indeed, epileptic subjects display (long) periods of normal electroencephalographic (EEG) activity (i.e., nonepileptiform) intermingled occasionally with epileptiform paroxysmal activity. Based on a computational model [3] we hypothesized that some types of epileptic transitions represent bifurcations occurring in a bistable system. Bistable systems feature two stable operational states that exist simultaneously for the same set of system's parameters. These states correspond to the attractors of the underlying dynamical system. One of these states is the normal, interictal state and the other state is the epileptic state of the network. We can assume that transitions between the states are relatively fast with respect to the times spent by the system in these states, therefore, the current state is always well defined. Transitions between the two states may occur due to an external stimulus (as, e.g., in cases of reflex epilepsy) or from the influence of random inputs and/or parameter fluctuations. We associate these noisy perturbations with a stochastic process although in certain conditions it may be not possible to distinguish such a process from a fast chaotic motion ([4]). In the simplest case, only the system's "fast" degrees of freedom participate in the transition (we call such systems *rigid* systems) and the transition can be modeled as a statistical *Poisson process*. Under these conditions the transitions between two discrete states have fixed probability of occurrence, much like the probability of a quantum transition in quantum mechanics. Accordingly, the distributions of duration of ictal and seizure-free epochs are exponential. Such system does not "memorize" anything more than the state (normal or epileptic) that it is currently in. In more complicated cases, the probability of a transition from one state to another depends on the time already spent in the current state, hence the system has a memory. The origin of such a memory can be assigned to the existence of "slow" dynamical degrees of freedom, for example plastic synaptic efficiencies. Under these circumstances, the times between transitions can be modeled by gamma distributions that are a generalization of the exponential distribution. The time dependence of the probability of transition may be different according to the underlying mechanisms. In one scenario, the system has fixed parameters but it can accumulate excitatory and inhibitory random inputs to reach a transition. In such a case, the resulting process consists of a sequence of discrete steps of fixed length and corresponds to a *random walk*. In an alternative scenario, in which *plastic* mechanisms are involved, one or more system parameters may change gradually after a transition, which may facilitate or counteract a subsequent transition. The aim of this paper was to identify the dynamical scenarios of transitions between normal and paroxysmal state in epileptic systems and possibly to detect the presence of slow, plastic mechanisms modulating

Manuscript received November 23, 2004; revised June 28, 2005. *Asterisk indicates corresponding author.*

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Digital Object Identifier 10.1109/TBME.2005.869800

0018-9294/$20.00 © 2006 IEEE

the transition probabilities. More specifically, we aim to quantify the deviation of certain classes of epileptic phenomena from the Poisson process and, thus, to deduce the presence of memory in the underlying system. In this paper, we analyze experimental time sequences from various animal models of absence epilepsy, human epileptic subjects and *in vitro* data. The analysis is based on the statistical properties of ictal and interictal epochs. The distributions of durations of normal and paroxysmal epochs are fitted with a gamma distribution, as a way of data reduction. On the basis of fitted parameters, we identify the dynamical processes that may have generated the underlying data. For a special case of a gamma distribution, the exponential distribution, as indicated above, we assume that the corresponding experimental data are generated by a rigid bistable system where transitions between states are induced by uncorrelated noise.

For a better interpretation of the experimental results we introduce a simple bistable mathematical model. It illustrates a system that can generate gamma statistics of transitions between two observable states. This model is purely metaphoric and its role is to help understanding the nature of the dynamics involved in bistable neurobiological systems on an abstract level and not to directly derive information about underlying epileptic process. However, if the model variable can be associated with a control parameter in a realistic neuronal network that governs transitions from normal to ictal states, then this could be an actual explanation of the measured gamma statistics. The model consists of a particle moving on a one-dimensional landscape with two minima (stable states). The particle is subject to fluctuations that can cause transitions between the two states. For different sets of model parameters the transitions may correspond to a Poisson process, to a random walk process or to deterministic transitions. The model allows for a better exploration of the correspondence between parameters of gamma distributions and underlying processes leading to transitions in a bistable system.

Understanding the dynamical properties of the system generating seizures can be relevant in the light of the recent attempts to predict time of seizure occurrence and develop electrical stimulation paradigms to prevent or abort an ictal state [5]. In a bistable rigid system, in which seizures are triggered by random fluctuations, the ictal transitions are unpredictable (per definition). Nevertheless, a single pulse [2] may terminate an ictal oscillatory state. In contrast, in a system with plasticity, the gradual changes leading to a seizure may be detectable some time before clinical manifestations and repetitive stimulation counteracting these changes may be effective in preventing or aborting an ictal state.

II. Materials and Methods

A. Patients

These five epileptic patients (mean age: 15 years, age range: 5–31 years, 2 women) underwent prolonged video-EEG monitoring investigations in the Epilepsy Monitoring Unit at Stichting Epilepsie Instellingen Nederland (Dutch Epilepsy Clinics Foundation), Heemstede, the Netherlands, during routine diagnostic work-up. Prior to digitization at a sampling rate of 200 Hz, EEG signals were filtered using a digital hardware antialiasing low-pass filter at 100 Hz. Using notch-filters, the 50 Hz powerline component was eliminated. The criterion for inclusion in the study was the presence of numerous ($>$50) focal seizures (patient 1) or frequent bursts ($>$3 per hour) of spike and wave discharges (SWD) with or without clinical symptoms (patients 2–5). Patients 1 and 2 had focal seizures consistent with frontal lobe origin as well as with structural pathology in these regions detected on magnetic resonance imaging (MRI) scans. Patients 3 through 5 had absence seizures and no abnormality in the MRI. Patient number 5 also exhibited a prominent photosensitivity and she was the only patient who was not taking antiseizure drugs at the time of the recording. In patient 1, day and night recordings were analyzed jointly in order to obtain sufficient data to create reliable statistics. In patients 2–5, day and night recordings were analyzed separately.

B. GAERS Rats

Recordings form Genetic Absence Epilepsy Rats from Strasbourg (GAERS) were obtained at the Laboratory for Clinical and Experimental Neurophysiology, Department of Neurology, Ghent University Hospital, Ghent, Belgium. The animals, all male GAERS, were 4–6 months of age and weighted between 300 and 330 g. We analyzed 9 different EEG fragments from 8 different rats (recordings #8 and #9 are from the same animal). The EEG was recorded by epidural peg electrodes for three to five consecutive hours during the light period of the day-night cycle. All animals were drug free at the time of the recording and were allowed free movement. No sensory stimulation was delivered to prevent sleeping. SWD were marked by an experienced clinician. Details of data acquisition and seizure detection can be found in [6].

C. WAG/Rij Rats

Recordings from Wistar albino Glaxo from Rijswijk (WAG/Rij) rats were obtained at the NICI/Department of Biological Psychology, University of Nijmegen, Nijmegen, the Netherlands. We analyzed recordings from drug free (saline) rats and from rats six hours after injection of vigabatrin (500 mg/kg). In total, nine rats were analyzed under saline conditions and five rats under vigabatrin. The seizures were scored during six hours for the saline condition and for 30 min for the vigabatrin condition, both during the dark period of the day-night cycle. From vigabatrin treated rats we selected for further analysis three rats that yielded more than 30 seizures in the observation period. Details of data acquisition and seizure detection are given in [7].

D. In Vitro Low Magnesium Models

1) Whole Hippocampal Recordings: Male C57/BL mice (P8-27) were anaesthetized with halothane and decapitated in accordance with the Canadian Animal Care Guidelines. The brain was extracted and placed in ice-cold, oxygenated ACSF and the hippocampus was dissected out. Hippocampi were transferred to oxygenated room-temperature ACSF for a minimum of 1.5 hours before being placed in a dual perfusion input recording chamber. This solution contained (in mM): 125 NaCl, 26 $\mathrm{NaHCO_3}$, 2.5 KCl, 1.8 $\mathrm{CaCl_2}$, 0.9 $\mathrm{MgCl_2}$, 1.25 $\mathrm{NaH_2\,PO_4}$, and 15 glucose. Epileptiform activity was obtained by perfusing the tissue with low-$\mathrm{Mg^{2+}}$ ACSF (0.25 mM). Extracellular field recordings were obtained from the CA1 cell

layer of the mid-hippocampal region and filtered (lowpass, 1 kHz), amplified and recorded (2 kHz). For a more detailed dissection methodology, see [8].

2) Hippocampal Slice Recordings: Wistar rats (P18-25) were anesthetized with halothane and decapitated in accordance with the guidelines of the Canadian Animal Care Committee. The brain was quickly removed and placed in ice-cold, continuously oxygenated ($95\%\ O_2 - 5\%\ CO_2$) artificial cerebrospinal fluid (ACSF). This solution contained (in mM): 125 NaCl, 26 $NaHCO_3$, 2.5 KCl, 1.8 $CaCl_2$, 0.9 $MgCl_2$, 1.25 NaH_2PO_4, and 10 glucose. Entorhinal cortex/hippocampal slices (500 μm thick) were incubated for at least 1 h before being transferred to an interface-type chamber for extracellular field recording in the CA1 hippocampal region, and recurrent spontaneous seizures were produced by perfusing the slices with low Mg^{2+} ACSF (0.5 mM). For a more detailed description of data acquisition see [9].

E. Automated Seizure Detection

We developed a simple automated method of seizure detection in human patients. First, the EEG signal was detrended by subtracting the local mean form the signal. The local mean was calculated by convoluting the original signal with a Gaussian kernel of small aperture (width at half maximum: 10–200 points). Subsequently, the detrended signal was squared and convolved again with a Gaussian kernel of larger aperture (25–500 points). Apertures were selected individually for each patient. The resulting signal represented an 'envelope' of the original signal where seizures were reflected by large amplitudes of that signal. The detection threshold was set individually for each patient such that it gave best results in comparison to visual inspection of the original signals. The method was applied to a single channel, which had the smallest number of artifacts (electrodes Pz or Fz). In patient 1, seizures were detected visually and marked by a qualified clinical neurophysiologist (D.V.).

F. Distribution Parameter Estimation

Both ictal and interictal durations distributions were fitted with a gamma distribution

$$y = Cx^{\alpha-1}e^{\frac{-x}{\beta}}$$

where α and β are distribution's parameters and C is a normalization constant. Gamma distributions are flexible in terms of their overall shape. The shape is determined by the shape parameter, α. For $\alpha < 1$, the distribution has the maximum at the origin and is monotonically decreasing, for $\alpha = 1$ the distribution has an exponential shape and for $\alpha > 1$, the distribution has zero at the origin and maximum at nonzero value. The fit was performed by procedure *gamfit* in Statistics Toolbox in Matlab, The Math Works Inc., Natick, MA, USA. This procedure yields the maximum likelihood estimation and 95% confidence intervals for the α and β parameters.

G. Mathematical Model

In order to better understand the basic process investigated here we constructed a formal model with bistability properties. This can be schematized by considering a ball with zero mass moving in a media with viscosity q and subject to a force generated by symmetric double-well potential: $U(x) = x^4 + ax^3 + bx^2$. The particle dynamics is also subjected to fluctuations induced by a zero-mean Gaussian noise $\xi(t)$. The time evolution of the particle's coordinate x is given by a Langevin equation

$$q\dot{x} = -\frac{\partial U(x)}{\partial x} + \xi(t).$$

Due to the fluctuations the ball may pass from one well to another. We consider that a passage from one state to another has taken place when the ball moved one-quarter of the way down to the other state. In order to simulate plastic effects playing a role in transitions between the two states we introduced a time dependence of parameter a

$$\dot{a} = -\lambda a + \mu x \frac{(A^2 - a^2)}{A^2}.$$

For $\mu > 0$, the evolution of parameter a, raises the well in which the ball is currently present and lowers the other one. For $\mu < 0$, the evolution of parameter a, lowers the current well and raises the other one. Changes of a are limited by parameter A.

We used fixed $b = -5$, $A = 5$, $\lambda = 0.5$ and varied q, μ and noise variance. For each parameter set we simulated 2000 transitions and fitted gamma distributions to the distributions of times spent in one of the states (due to symmetry of the potential, distributions for both states were almost identical).

III. Results

A. Distributions of Durations of Ictal and Interictall Epochs

The α parameter of the gamma distributions fitted to the histograms of durations of ictal epochs are given in Table I, third column. Graphical presentation of the values of the α parameter for ictal epochs is shown in Fig. 1. The horizontal line on Fig. 1 denotes a value of $\alpha = 1$. In some cases (patient 2, 3, GAERS 2, 5, 9, all WAG/Rij vigabatrin rats), the 95% confidence intervals include $\alpha = 1$. In those cases, the data can be described by an exponential distribution and the null hypothesis of a Poisson process cannot be rejected at the significance level 5%. In other cases (patient 1, 4, 5, GAERS 1, 3, 4, 6, 7, 8, all WAG/Rij rats saline, all hippocampal recordings), the α parameter is significantly larger than one. In the latter cases, ictal epochs have predominantly fixed duration and their distributions exhibit a pronounced maximum corresponding to a deterministic component; thus, the hypothesis of a Poisson process operating in a bistable system can be rejected.

The α parameter of the gamma distributions fitted to the histograms of durations of interictal epochs are given in Table I, fifth column. Graphical presentation of the values of the α parameter for interictal epoch is shown in Fig. 2. The horizontal line denotes a value of $\alpha = 1$. In a minority of cases (patient 1, 2, 5 day, GAERS 5, all WAG/Rij rats saline, WAG/Rij vigabatrin rat 3, hippocampal slice (S) recording), the 95% confidence intervals of the α parameter include the unity value of α. In these cases, the data are well described by an exponential distribution and the null hypothesis of a Poisson process ($\alpha = 1$) cannot be rejected at the significance level 5%. In other cases (patient 3, 4, 5 night, all GAERS except 5, all WAG/Rij rats saline, WAG/Rij rats vigabatrin 1, 2), the α parameter is significantly smaller than one and the hypothesis of a Poisson process can be rejected. In the low magnesium *in vitro* model, whole hippocampal recordings (W) the α parameter is much larger than one. Such a value

TABLE I

SUMMARY OF THE DATA USED AND CORRESPONDING α PARAMETER VALUES FOR DIFFERENT EXPERIMENTAL CONDITIONS. COLUMNS THREE AND FIVE GIVE GAMMA DISTRIBUTION PARAMETER α WITH 95% CONFIDENCE INTERVALS (CI) OF THE DURATIONS OF ICTAL AND INTERICTAL EPOCHS, RESPECTIVELY. MEDIAN DURATION WITH 25TH AND 75TH PERCENTILE (P25–P75) OF THE CORRESPONDING ICTAL AND INTERICTAL EPOCHS ARE GIVEN IN COLUMNS FOUR AND SIX, RESPECTIVELY. LAST TWO COLUMNS GIVE THE NUMBER (N) OF ANALYSED EPOCHS AND THE TOTAL DURATION T_{tot} (IN HOURS) OF THE EEG RECORDINGS USED

		Ictal		Interictal			
Group		α (CI)	Median(P25-P75)	α (CI)	Median (P25-P75)	N	T_{tot}
Patient 1		6.39 (3.42 - 9.36)	21 (17 - 29)	0.99 (0.10 - 1.89)	1020 (652 – 3338)	30	20.1
Patient 2	Day	0.82 (0.54 - 1.09)	2.2 (1.2 – 4.7)	0.82 (0.59 - 1.05)	22.5 (6.3 - 50.2)	126	8.6
	Night	0.85 (0.65 - 1.05)	7.1 (3.6 - 19.2)	0.83 (0.65 - 1.00)	4.6 (2.7 – 8.5)	205	2.6
Patient 3	Day	1.32 (0.75 - 1.89)	1.6 (0.5 - 2.87)	0.35 (0.24 - 0.47)	86.0 (20.7 - 390.7)	83	11.8
	Night	1.14 (0.96 - 1.33)	0.8 (0.4 - 1.7)	0.46 (0.39 - 0.53)	18.9 (4.1 - 60.4)	352	5.8
Patient 4	Day	4.75 (3.14 - 6.37)	1.4 (1.1 - 2.2)	0.58 (0.44 - 0.72)	264.6 (99.5 -667.7)	74	11.3
	Night	2.45 (1.88 - 3.02)	0.8 (0.6 - 1.2)	0.44 (0.33 - 0.55)	88.1 (31.9 - 179.4)	124	9.9
Patient 5	Day	6.57 (5.84 - 7.31)	3.1 (2.3 – 4.2)	1.12 (0.99 - 1.25)	46 (19 – 81)	495	8.8
	Night	2.95 (2.24 - 3.66)	3.3 (2.7 – 4.8)	0.65 (0.51 – 0.79)	62 (21.5 – 164)	173	11.8
GAERS	1	1.51 (1.19 - 1.84)	15.7 (7.9 - 28.4)	0.50 (0.41 - 0.67)	12.5 (3.3 - 34.1)	186	3
	2	1.21 (0.93 - 1.48)	10.6 (5.1 - 22.9)	0.51 (0.37 - 0.65)	10.1 (4.8 - 21.7)	212	3.2
	3	1.35 (1.08 - 1.62)	51.7 (25.6 - 99.1)	0.58 (0.47 - 0.71)	55.6 (17.2 - 174.3)	256	28
	4	1.82 (1.53 - 2.10)	7.7 (4.5 - 13.8)	0.45 (0.35 - 0.56)	12.3 (4.7 - 28.9)	306	5.6
	5	2.45 (0.95 - 3.96)	14.8 (7.6 - 22.5)	0.94 (0.52 - 1.36)	54.2 (18.6 - 99.7)	31	0.8
	6	2.05 (1.78 - 2.33)	9.3 (5.3 - 14.5)	0.51 (0.43 - 0.59)	12.9 (4.5 - 29.7)	394	5.9
	7	2.23 (1.91 - 2.54)	6.3 (3.8 - 10.1)	0.67 (0.58 - 0.76)	10.6 (5.1 - 26.4)	486	5.9
	8	1.76 (1.13 - 2.39)	6.7 (4.2 - 12.9)	0.41 (0.17 - 0.64)	6.9 (2.5 - 26.4)	66	1.1
	9	1.33 (0.89 - 1.77)	8.4 (4.1 - 19.7)	0.38 (0.22 - 0.55)	10.6 (4.1 - 35.7)	117	3.1
WAG/Rij	1	3.58 (2.16 - 5)	6.9 (4.7 - 9.6)	0.42 (0.23 - 0.61)	59.3 (17.2 - 409.5)	60	5.6
- saline	2	4.72 (3.66 - 5.79)	4.7 (3.6 - 6.6)	0.53 (0.34 - 0.72)	56.9 (23.2 - 195.6)	98	5.9
	3	3.60 (2.89 - 4.32)	4.5 (3.1 - 6.4)	0.47 (0.33 - 0.62)	21.6 (10.5 - 107.3)	170	5.9
	4	4.22 (2.97 - 5.49)	6.3 (3.9 - 8.3)	0.59 (0.39 - 0.81)	58.9 (23.4 - 273.)1	95	5.7
	5	2.63 (1.80 - 3.47)	5.1 (3.4 - 8.5)	0.51 (0.29 - 0.73)	92.0 (27.4 - 284.2)	66	5.9
	6	3.17 (2.54 - 3.81)	5.0 (3.7 - 6.7)	0.42 (0.27 - 0.58)	31.7 (9.9 - 156.9)	108	5.9
	7	4.48 (3.16 - 5.80)	5.4 (3.9 - 6.8)	0.44 (0.27 - 0.62)	50.5 (22.7 - 237.3)	75	5.8
	8	3.93 (2.92 - 4.94)	4.4 (3.1 - 6.3)	0.53 (0.36 - 0.70)	66.2 (25.5 - 150.9)	100	5.6
	9	3.47 (2.69 - 4.26)	5.8 (4.4 - 8.2)	0.53 (0.34 - 0.71)	50.8 (14.9 - 211.8)	106	5.7
WAG –	1	1.14 (0.70 - 1.58)	11.4 (3.7 - 19.9)	0.56 (0.25 - 0.87)	2.7 (1.1 - 5.3)	53	0.3
vigabatrin	2	0.93 (0.57 - 1.28)	5.7 (1.3 - 12.1)	0.42 (0.15 - 0.68)	4.3 (1.8 - 11.9)	54	0.5
	3	1.11 (0.85 - 1.36)	3.3 (1.5 - 5.8)	1.06 (0.85 - 1.28)	2.4 (1.2 – 4.3)	181	0.5
Mg	W	1.94 (1.36 - 2.53)	5.5 (3.9 - 9.3)	2.01 (1.48 - 2.53)	9.4 (5.8 - 12.7)	70	0.3
	S	1.42 (1.20 - 1.63)	3.6 (2.3 - 5.1)	1.01 (0.80 - 1.21)	2.6 (1.1 - 7.6)	224	0.7

GAERS—Genetic Absence Epilepsy Rats from Strasbourg, WAG/Rij—Wistar Albino Glaxo from Rijswijk, Mg—Low magnesium hippocampal model, "W"—Whole hippocampal recording, "S"—Hippocampal slice recording.

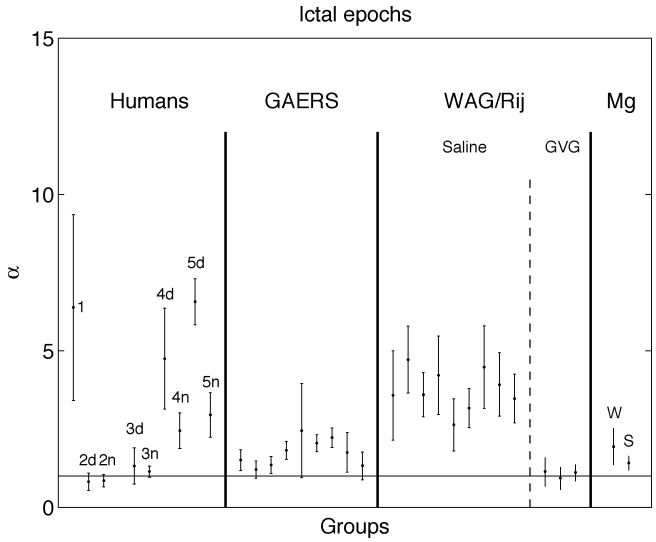

Fig. 1. Graphical presentation of the values of shape parameter, α, with 95% confidence intervals of gamma distribution of ictal epochs for different experimental conditions. The horizontal line denotes value of $\alpha = 1$. In cases when 95% confidence intervals include $\alpha = 1$, the termination of ictal epochs is consistent with a Poisson process. Numbers on the graph denote number of patients. Abbreviations: "d"—daytime recording, "n"—nighttime recording, GAERS—Genetic Absence Epilepsy Rats from Strasbourg, WAG/Rij—Wistar albino Glaxo from Rijswijk, GVG—vigabtarin, Mg—low magnesium hippocampal model, "W"—whole hippocampal recording, "S"—hippocampal slice recording.

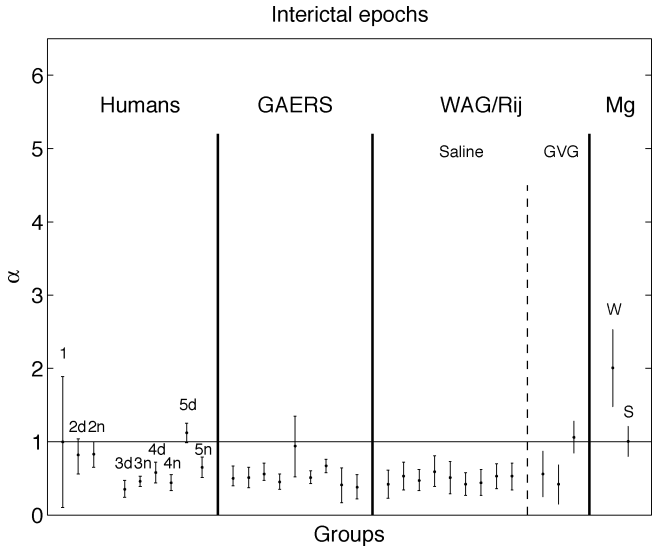

Fig. 2. Graphical presentation of the values of shape parameter, α, with 95% confidence intervals of gamma distribution of interictal epoch for different experimental conditions. The horizontal line denotes value of $\alpha = 1$. In cases when 95% confidence intervals include $\alpha = 1$, the initiation of ictal epochs is consistent with a Poisson process. Finding $\alpha < 1$ at 95% confidence intervals suggest that seizure initiation occurs according to a random walk process. Numbers on the graph denote number of patients. Abbreviations: "d"—daytime recording, "n"—nighttime recording, GAERS—Genetic Absence Epilepsy Rats from Strasbourg, WAG/Rij—Wistar albino Glaxo from Rijswijk, GVG—vigabtarin, Mg—low magnesium hippocampal model, "W"—whole hippocampal recording, "S"—hippocampal slice recording.

suggests the presence of a deterministic mechanism pacing the occurrence of epileptiform discharges under those conditions.

Examples of experimental distributions with $\alpha < 1$, $\alpha = 1$, $\alpha > 1$ are presented in Fig. 3(a)–(c), respectively. Despite the horizontal scale of Fig. 3(a) is different from that of Fig. 3(b),

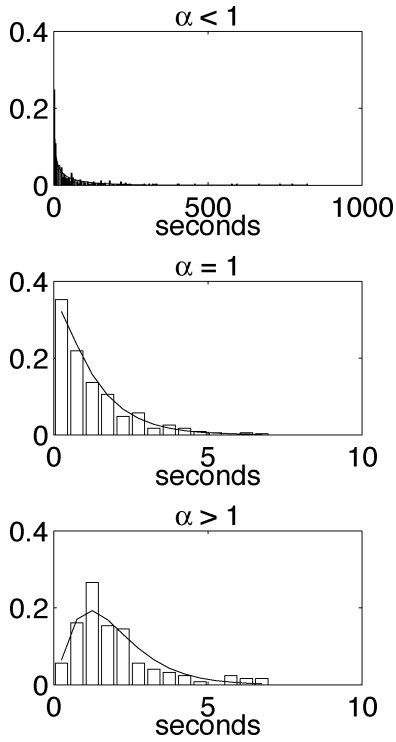

Fig. 3. Examples of experimental distributions with different values of shape parameter. (a) $\alpha < 1$. (b) $\alpha = 1$. (c) $\alpha > 1$. In each panel, experimental distribution and fitted gamma function are shown. (a). Distribution of interictal epochs during a night in patient 3 ($\alpha = 0.46$). (b). Distribution of ictal epochs during a night in patient 3 ($\alpha = 1.14$). (c). Distribution of ictal epochs during a night in patient 4 ($\alpha = 2.45$).

(c), the qualitative differences between the graphs are clear. Distribution with $\alpha < 1$ [Fig. 3(a)] has very long tail, which is not present for $\alpha = 1$ [Fig. 3(b)] and $\alpha > 1$ [Fig. 3(c)]. Distribution with $\alpha > 1$ [Fig. 3(c)] has maximum at nonzero value, while distributions with $\alpha < 1$ [Fig. 3(a)] and $\alpha = 1$ [Fig. 3(b)] have maximum at the origin. To establish whether α values are related to the durations of the analyzed epochs we calculated linear correlation coefficient between the values of shape parameter and median epochs duration. For both ictal and interictal groups, the correlations were not significant ($p > 0.05$).

B. Mathematical Model

The results of simulations of the mathematical model are shown in Fig. 4. Fig. 4(a) shows the dependence of parameter α on the viscosity parameter q. The plasticity was not included ($\mu = 0$) and the noise standard deviation was high (15). For the low values of viscosity and large fluctuations, the system exhibits discrete jumps between the two states. In such a case, the transition represents a Poisson process and the distribution of inter-transition intervals is exponential as indicated by values of α close to one. As viscosity increases, the random inputs accumulate in the course of time and the transition represents a random walk process. This is reflected in values of $\alpha < 1$.

Fig. 4(b) shows values of the parameter α when plastic mechanisms (parameter $\mu \neq 0$) were included. In all simulations shown here, viscosity was low ($q = 0.2$) to rule out random walk effects and noise standard deviation was small (7.5) to slow down the transition rate and allow plastic changes to take effect. For negative values of the plasticity parameter μ, the system

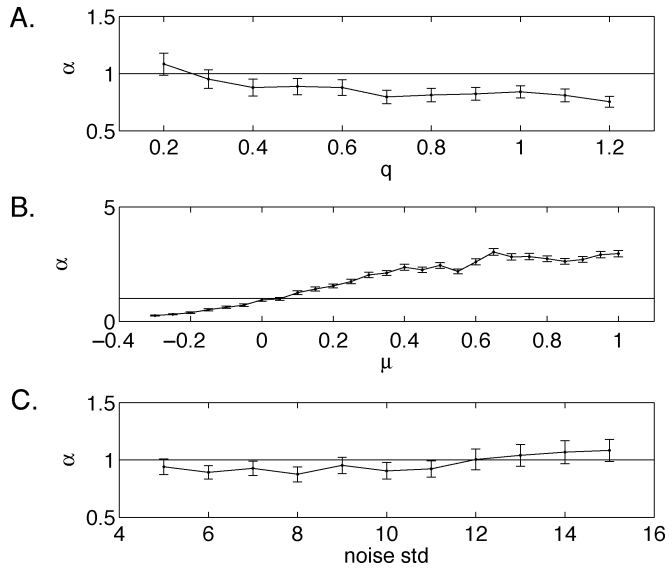

Fig. 4. Result of the mathematical model. (a) Dependence of the parameter α on the viscosity parameter q. For low viscosity, single fluctuation can move the ball from one minimum to another and the transitions are of a Poisson process type with α close to one. For increasing viscosity the ball accumulates inputs to reach a transition and the system is of a random walk type with α smaller than one. (b) Dependence of parameter α on plasticity parameter μ. For negative μ, plasticity tends to maintain the current state, which results in a random walk type of process with $\alpha < 1$. For positive values of plasticity, the deterministic process tends to terminate the current state which results in $\alpha > 1$. (c) Dependence of the parameter α on standard deviation (std) of the noise. For different noise levels α is close to one. It shows that α parameter is not sensitive to size of the fluctuations.

lowers the minimum where the ball currently is present, which serves as a deterministic mechanism that progressively counteracts a transition to the other state. Accordingly, the chance of a transition decreases as a function of the duration contrary to the case of Poisson process, where the chance of the transition is constant. This fact is quantitatively reflected by values of $\alpha < 1$.

For positive values of the plasticity parameter μ, the system raises that minimum of the potential function where the ball currently is present. Therefore, apart from random fluctuations, there is also a deterministic mechanism that progressively facilitates a transition to the other state. Accordingly, the times spent in each of the states exhibit random variation around a fixed component. This is reflected in the duration distribution having a single peak at nonzero value as indicated by values of $\alpha > 1$. With increasing values of μ the contribution of the fixed component increases and the transitions progressively attain periodicity as reflected by increasing values of the parameter α.

Fig. 4(c) shows values of α parameter for low viscosity ($q = 0.2$), no plasticity ($\mu = 0$) and different values of standard deviation (std) of the noise. With increasing noise, α remains close to one. This shows that α is not sensitive for the level of noise. The size of the fluctuations influences mainly the scale parameter, β (not shown here).

IV. Discussion

The aim of this paper is to infer dynamical features of a neuronal system from the distribution of event and inter-event durations generated in that system. We analyzed experimental data from human epilepsies (both localization related and generalized), animal models and an *in vitro* model. We followed a parametric approach, in which distributions of ictal and interictal epochs were fitted with two-parameter gamma distributions. According to the value of the fitted shape parameter, transitions in the underlying system were classified as being consistent with a Poisson process, a random walk process or a deterministic process involving plasticity.

Despite the fact that epileptic data analyzed here were very diverse a clear and consistent pattern emerged from the results. This is an interesting finding by its own because it shows that various epileptic models can be classified into only few different dynamical classes and that several distinct epilepsies may share the same underlying dynamics of ictal transitions. The first general outcome of the analysis is that in a number of ictal and interictal data the null hypothesis of a bistable system with purely random leaps cannot be rejected. Those cases are identified by parameter α close to one, which implies that the duration distribution is exponential. As derived analytically [10] exponential distribution of intervals between events follows from a Poisson process, in which events occur along time with constant probability rate of occurrence. Table I and Figs. 1 and 2 show that the distribution's shape parameter, α, can be close to one in both ictal and interictal recordings. The second result is that the dynamical processes obtaining during ictal epochs are, in general, different that those obtaining during the interictal state. A majority of ictal epochs have an α parameter larger than one. It suggests that deterministic time—dependent mechanisms are involved in seizure termination and the probability of terminating an ictal state increases with time spent already in that state. On the contrary, interictal epochs are described predominantly with α parameter smaller than one. It suggests that the longer the system remains in a seizure free state the higher the chance it shall remain seizure free in the immediate future. This kind of dynamics results in a grouping of seizures, i.e., in the appearance of clusters of ictal episodes separated by long interictal periods. Seizure clustering was also reported in other studies. In [11], data from epileptic patients with different seizure types were analyzed. In half of the patients, seizure occurrence was indistinguishable from a Poisson process while other patients showed seizure clustering. In [12], dependencies between seizure occurrences were found in patients with complex partial seizures, ruling out the hypothesis of a homogenous Poisson process. The former study used seizure diaries maintained for a number of days while the latter study used seizure times recorded over 1–3 years. Despite obvious differences with these studies our findings seem to corroborate at least some of the earlier results. One should note that our study refers to a different time scale of observation since we analyzed human seizure patterns in continuous 24 hour recordings.

A clear exception from the rules that apply to interictal epochs in humans and rats is the *in vitro* low Mg^{+2} model. The α parameter describing the distribution of interictal intervals in whole hippocampal recordings is larger than one (Fig. 2). It shows that occurrence of ictal epochs have some periodicity, which is consistent with experimental observations [8]. This is, however, in contrast to all other interictal recordings analyzed here. One might also consider that larger alpha values are related to shorter durations of the epochs analyzed. However, our linear correlation analysis gave no indication for such a relationship.

The current analysis offers some clues regarding the physiological mechanisms responsible for seizure termination. For instance in all patients with absence seizures (3, 4, 5) recordings during daytime yield higher values of α than those during nighttime. Such a variation suggests that at least in these patients and perhaps in idiopathic generalized epilepsy (IGE) expressing itself with absence seizures, deterministic mechanisms of seizure termination are predominantly operating during wakefulness. A close relationship to the sleep-waking cycle is present in patients with IGE [13] that might possibly be hormonally regulated [14]. The extent to which seizure stopping mechanism operates may also vary between the subjects, even of the same epilepsy type. This could explain the quantitative differences between values of α for patients 3–5. A marked difference in alpha value of distributions of ictal epochs in patients 1 and 2, both suffering from the frontal lobe epilepsy, together with differences in durations of ictal and interictal epochs (see Table I) may reflect the clinical observations that nocturnal frontal lobe epilepsy syndrome encompasses heterogeneous group of patients with various seizure types (see [15]). However, in the latter study the authors reported also a remarkable stereotypy in all types of attacks in all patients. While seizures in patient 1 have stereotyped durations, reflected by value of alpha much larger than one, seizures in patient 2 seem to lack homogeneity in their durations (alpha around one). One cannot exclude that patient 2 displayed more than one type of epileptic attack, which is common in this type of epilepsy [15].

In WAG/Rij rats, a model with certain similarities with human absence epilepsy, the α parameter is larger than one in all saline rats, while α is equal to one in all vigabatrin treated animals. Such change of the value of α suggests that time-dependent mechanisms of seizure termination, present under normal conditions, are turned off after vigabatrin administration. A more extensive interpretation of these results in physiological terms is beyond the scope of this study and shall be discussed elsewhere.

Results of the simulations of the simple mathematical model are relevant in two respects. First, they show that the value of the shape parameter of a gamma distribution can help to distinguish transitions occurring according to a Poisson process from those in which transition probability varies with time. Only the former conditions yield values of α close to one while in all other cases, α exhibited deviation from unity (Fig. 4). Second, the model indicates that when α deviates from one, the interpretation of experimental results may be not straightforward. Values of α smaller than one may arise either due to continuous random walk process [Fig. 4(a)] or due to deterministic changes counteracting the transitions [Fig. 4(b)]. These two mechanisms, that probably correspond to quite different physiological substrates, result in fact in the same type of process if one considers the combined dynamics of x and a. The only distinction between "plastic" parameters and "ordinary" dynamic degrees of freedom is their different scale of time-evolution. Values of $\alpha > 1$ suggest the presence of plastic mechanisms that act to abort the current state [Fig. 4(b). Alternatively, a gamma distribution with of $\alpha > 1$ can also arise from the sum of exponentially distributed random variables having equal means [16]. The interpretation of experimental results with $\alpha > 1$ is therefore, in strict terms, not unique.

Identification of dynamical scenarios leading to the appearance of paroxysmal episodes may help to establish whether the occurrence of this type of phenomena can be predicted. Our results suggest that seizure onset is associated with either a Poisson or a random walk type of process and that such may differ depending on whether one is dealing with localization-related epilepsy with a focal seizure disorder or with an IGE with an absence seizure disorder. It implies that prediction of the exact timing of seizure occurrence is not possible. However, quantifying the probability for seizure transition by monitoring changes of the system's excitability may be feasible [17].

Understanding the dynamical mechanisms underlying the occurrence of epileptic seizures in selected cases may afford the possibility to abort an ictal state by appropriate counter stimulation when applicable. In bistable systems where a stable steady-state coexists with a stable limit cycle, for instance, the abnormal rhythm may be terminated by a single well-timed pulse [2]. We demonstrated an effective single pulse counter-stimulation in our computational model, which exhibited bistability properties [3].in an earlier study [3]. However, seizures belonging to different dynamical classes my require different stimulation approaches. Therefore, application of the general method of establishing dynamical properties of the epileptic system presented in this study may be an important step to design appropriate seizure control paradigm.

In summary, our analysis of the temporal distributions of both interictal epochs and epileptic seizures may provide additional insight into the dynamical nature of the underlying pathophysiological system. In general, although seizure initiation appears to be governed by a stochastic (Poisson or random walk) process seizure termination often involves deterministic mechanisms. Reconstruction of fundamental dynamical laws governing the behavior of an epileptic system in time is a powerful tool both for inferring knowledge on the system's future behavior and for developing appropriate and rational therapeutic strategies.

REFERENCES

[1] F. H. Lopes da Silva, W. Blanes, S. N. Kalitzin, J. Parra, P. Suffczynski, and D. N. Velis, "Dynamical diseases of brain systems: different routes to epileptic seizures," *IEEE Trans. Biomed. Eng.*, vol. 50, no. 5, pp. 540–548, May 2003.

[2] L. Glass and M. C. Mackey, *From Clocks to Chaos: The Rhythms of Life*. Princeton, NJ: Princeton Univ. Press, 1988.

[3] P. Suffczynski, S. N. Kalitzin, and F. H. Lopes da Silva, "Dynamics of nonconvulsive epileptic phenomena modeled by a bistable neuronal network," *Neuroscience*, vol. 126, pp. 467–484, 2004.

[4] H. Kantz, W. Just, N. Baba, K. Gelfert, and A. Riegert, "Fast chaos versus white noise: entropy analysis and a Fokker-Planck model for the slow dynamics," *Physica D*, vol. 187, pp. 200–213, 2004.

[5] L. D. Iasemidis, "Epileptic seizure prediction and control," *IEEE Trans. Biomed. Eng.*, vol. 50, no. 5, pp. 549–558, May 2003.

[6] P. van Hese, J. P. Martens, P. Boon, S. Dedeurwaerdere, I. Lemahieu, and R. van de Walle, "Detection of SWD in the cortical EEG of GAERS," *Phys. Med. Biol.*, vol. 48, pp. 1685–1700, 2003.

[7] B. M. Bouwman, P. L. C. van den Broek, E. L. J. M. van Luijtelaar, and C. M. van Rijn, "The effects of vigabatrin on type II spike wave discharges in rats," *Neurosci. Lett.*, vol. 338, pp. 177–180, 2003.

[8] M. Derchansky, E. Shahar, R. A. Wennberg, M. Samoilova, S. S. Jahromi, P. A. Abdelmalik, L. Zhang, and P. L. Carlen, "Model of frequent, recurrent and spontaneous seizures in the intact mouse hippocampus," *Hippocampus*, vol. 14, no. 8, pp. 935–947, 2004.

[9] H. Khosravani, P. L. Carlen, and J. L. Velazquez, "The control of seizure-like activity in the rat hippocampal slice," *Biophys. J.*, vol. 84, pp. 687–695, 2003.

[10] J. L. Doob, *Stochastic Processes*. New York: Wiley, 1953.

[11] J. G. Milton, J. Gotman, G. M. Remillard, and F. Andermann, "Timing of seizure recurrence in adult epileptic patients: a statistical analysis," *Epilepsia*, vol. 28, pp. 471–478, 1987.

[12] L. D. Iasemidis, L. D. Olson, R. S. Savit, and J. C. Sackellares, "Time dependencies in the occurrence of epileptic seizures," *Epilepsy Res.*, vol. 17, pp. 81–94, 1994.

[13] F. Andermann and S. F. Berkovic, "Idiopathic generalized epilepsy with generalized and other seizures in adolescence," *Epilepsia*, vol. 42, pp. 317–320, 2001.
[14] S. H. Lin, A. C. Arai, R. A. Espana, C. W. Berridge, F. M. Leslie, J. R. Huguenard, M. Vergnes, and O. Civelli, "Prolactin-releasing peptide (PrRP) promotes awakening and suppresses absence seizures," *Neuroscience*, vol. 114, pp. 229–238, 2002.
[15] F. Provini, G. Plazzi, P. Tinuper, S. Vandi, E. Lugaresi, and P. Montagna, "Nocturnal frontal lobe epilepsy; a clinical and polygraphic overview of 100 consecutive cases," *Brain*, vol. 122, pp. 1017–1031, 1999.
[16] D. R. Cox and P. A. W. Lewis, *The Statistical Analysis of Series of Events*. London, U.K.: Chapman & Hall, 1978.
[17] S. N. Kalitzin, D. N. Velis, P. Suffczynski, J. Parra, and F. H. Lopes da Silva, "Intermittent electrical brain-stimulation paradigm for estimating the seizure onset site and the time to ictal transition in temporal lobe epilepsy," *Clin. Neurophysiol.*, vol. 116, no. 3, pp. 718–728, 2005.

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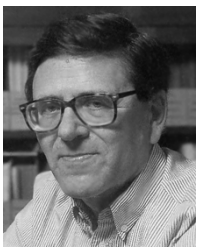

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