Geometric Models, Fiber Bundles and Biomedical Applications

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In this paper we explore the use of dynamical system techniques, geometric methods and experimental approaches to estimate the characteristics of brain electrical activity. We assume that the diagnostic information is in the form of a nonlinear time series. Then we sequentially apply a geometric approach for characterizing dynamical instability, based on a nonlinear estimation of dynamical characteristics. In addition to characterizing epileptic seizures, we discuss other diagnostically useful topics including the T-index of the short-term maximum Lyapunov exponents (STLmax) among critical sites of the cerebral cortex. Dynamical instability is here related to curvature fluctuation of the manifolds where geodesics are natural motion and is described by means of the Jacoby–Levi-Civita geodesic spread. The methods are illustrated using EEG data previously recorded from transgenic epileptic mouse.

1 Introduction

Epilepsy, among the most common disorders of the nervous system, affects approximately 1 % of the population [1–3]. About 25 % of the patients with epilepsy have seizures that are resistant to medical therapy [4]. Epileptic seizures result from a transient electrical discharge of the brain. These discharges often spread first to ipsilateral, then to contralateral cerebral cortex, thereby disturbing normal brain function. Clinical effects may include motor, sensory, affective, cognitive, automatic and physical symptomatology. The occurrence of an epileptic seizure appears to be unpredictable and the underlying mechanisms that cause seizures to occur are poorly understood. A recent approach in epilepsy research is to investigate the underlying dynamics that account for the physiological disturbances in the epileptic brain [5–7].

One of the most promising approaches to understanding of the dynamics of epilepsy is to determine the dynamical properties of the EEG signal generated by the epileptic brain. The traditional technique used to solve this problem in time series analysis is to fit a linear model to the data, and determine the optimal order (*dimension*) and the *optimal parameters* of the model. A simple generalization is to fit the best nonlinear dynamical model. However, the results of applying this methodology are usually not very illuminating. Without any prior knowledge, any model that we fit is likely to be *ad hoc*. We are more interested in questions as the following: How nonlinear is the time series? How many degrees of freedom does it have?

The present study was undertaken to develop a geometric methodology for estimating dynamical characteristics of an EEG time series and classifying the physiological state (e.g., interseizure state, pre-seizure state, seizure state and post-seizure state) of the human epileptic brain. This can be accomplished by employing a computer based algorithm that continuously estimates multiple dynamical measures from the input EEG time series. In addition, in order to create a modeling technique that incorporates existing information and can be interpreted neurodynamically (robust to noise), we propose a technique based on a combination of *dynamics*, *geometry*, and *fiber bundles*.

2 Geometrization of the brain dynamics

During the past decade, there has been growing evidence of the independence of the two properties of instability and predictability of the human brain dynamics. The generic situation of the brain dynamics is instability of the trajectories in the Lyapunov sense. Nowdays such instability is called intrinsic stochasticity, or chaoticity, of the brain dynamics and is caused by nonlinearity of the equation of motion.

In order to characterize the dynamical instability, we first examined some properties that characterize the EEG signal, including the spectrum of Lyapunov exponents, the energy, geodesics and fiber bundles. We analyze the parameter spaces as well as related quantities of T-index of STLmax, Jacoby–Levi-Civita equation, and modeling of EEG time series from the experimental point of view.

2.1. Spectrum of Lyapunov exponents. The leading Lyapunov exponent [9] λ is defined as:

$$\lambda_1(x_0) = \lim_{t\to\infty}\lim_{\epsilon\to 0}\frac{1}{t}\log\left(\frac{\|\langle y(t)\rangle - \langle x(t)\rangle\|}{\epsilon}\right), \tag{1}$$

where $y(t)$ and $x(t)$ are experimental time series of the dynamical system with two initial conditions $y(0)$ and $x(0)$; $\langle y(t)\rangle$ and $\langle x(t)\rangle$ are ensemble averages; $\|\langle y(t)\rangle - \langle x(t)\rangle\|$ is the Euclidean distance between $\langle y(t)\rangle$ and $\langle x(t)\rangle$; $\epsilon = \|\langle y(0)\rangle - \langle x(0)\rangle\|$. The equation (1) remains well defined in the presence of noise.

To characterize the dynamics from the observed EEG data $x(t)$ we need to find the local Lyapunov exponents using the local Jacobian matrix and the Oseledec matrix. The eigenvalues of the Oseledec matrix tell us how rapidly perturbations to the orbit at point x in phase space grow or shrink in P time steps away from the time of the perturbation. These $\lambda_i(x,P)$ are called the local Lyapunov exponents or the finite time Lyapunov exponents [9, 11].

The Lyapunov exponents provide a coordinate-independent measure of the asymptotic local stability of EEG data. The trajectories of an N dimensional state space have N Lyapunov exponents. These N Lyapunov exponents are often called the Lyapunov spectrum [9]. The qualitative features of the asymptotic local stability properties can be summarized by the sign of each Lyapunov exponent. A positive Lyapunov exponent indicates an unstable direction; a negative exponent indicates a stable direction. Thus $(+,-,-)$ implies a trajectory in three-dimensional state space with one positive Lyapunov exponent. The Lyapunov numbers Λ_i are defined as

$$\Lambda_i \equiv e^{\lambda_i}. \tag{2}$$

The Lyapunov spectrum and the metric entropy are related by Pesin's identity [14]

$$h_\mu = \sum_{i=1}^{r} \text{positive } \lambda_i, \tag{3}$$

where λ_i represents the Lyapunov exponents and r is the maximal number of positive Lyapunov exponents.

2.2. Lyapunov dimension. The Lyapunov dimension is a characteristics related to the spectrum of Lyapunov exponents and predictability of the EEG signal. The hypersurface of dimension m of the EEG signal expands at a rate governed by the sum $\sum_{i=1}^{m} \lambda_i$, where m is the embedding dimension. Kaplan and Yorke [12] have suggested the following definition of the Lyapunov dimension

$$d_L = k + \frac{\sum_{i=1}^{k} \lambda_i}{|\lambda_{k+1}|}, \tag{4}$$

where k is the largest value such that $\sum_{i=1}^{k} \lambda_i > 0$, and the second term characterizes the fractional part of the dimension. We may anticipate that for an epileptic attractor, the Lyapunov dimension is equal to the information dimension.

2.3. Geometric models and fiber bundles. This approach involves a geometric description of Lyapunov exponents for correcting the nonlinear process that provides adaptive dynamic control.

We separate the Lyapunov exponents into tangent space (fiber bundle) and its functional space. Control involves signal processing, calculation of an information characteristic, measurement of Lyapunov exponents, and feed-back to the system. With more information, we can reduce uncertainty by a certain degree.

We have demonstrated the computational aspects of the proposed geometric approach on the base of different mathematical models in the presence of noise of various origins [10]. We review the EEG signal, and outline a typical application of the geometrical representation: three dimensional reconstruction of Lyapunov exponents and correlation dimension obtained from EEG data.

The novelty in this report is in the representation of the dynamical instability by a Riemannian theory in a way that permits practical applications. We discuss an application of this approach to the development of novel devices for seizure control through electromagnetic feed-back.

2.4. Geometric description of dynamical instability. The actual interest of the Riemannian formulation of dynamics stems from the possibility of studying the instability of the brain dynamics through the instability of geodesics of a suitable manifold, a circumstance that has several advantages.

First of all, a powerful mathematical tool exists to investigate the stability or instability of a geodesic flow: the Jacobi—Levi-Civita (JLC) equation for geodesic spread.

The JLC equation describes covariantly how nearby geodesics locally scatter and is a familiar object in both Riemannian geometry and theoretical physics.

Moreover, the JLC equation relates the stability or instability of a geodesic flow with curvature properties of the ambient manifold, thus opening a wide and largely unexplored field for investigation, as far as physical systems are concerned, of the connections among geometry, topology, and geodesic instability.

Geometrization of the brain dynamics includes the following stages: 1) reconstruction of equations of the epileptic brain from experimental data; 2) realization in local coordinates of a one-parameter group of diffeomorphisms of a manifold M; 3) estimation of the largest Lyapunov exponent; 4) geometrization of the dynamics; 5) geometric description of the dynamical instability; 6) applying Jacobi–Levi-Civita equation for geodesic spread; 7) analytical description of the largest Lyapunov exponent.

2.5. An analytic formula for the largest Lyapunov exponent. By transforming the Jacobi–Levi-Civita equation from geodesic spread into a scalar equation for ψ variable, the original complexity of the JLC equation has been considerably reduced: from a tensor equation we have obtained an effective scalar equation formally representing a stochastic oscillator [13].

Our Lyapunov exponent is defined as

$$\lambda = \lim_{t \longrightarrow \infty} \frac{1}{2t} \ln \frac{\psi^2(t) + \dot{\psi}^2(0)}{\psi^2(0) + \dot{\psi}^2(0)}, \tag{5}$$

where $\psi(t)$ is solution of the equation

$$\frac{d^2\psi}{ds^2} + \Omega(t)\psi = 0, \tag{6}$$

$\Omega(t)$ is a Gaussian stochastic process;

$$\Omega(t) = \langle k_R \rangle_\mu + \mu \frac{1}{\sqrt{N}} \langle \delta^2 K_R \rangle_\mu^{\frac{1}{2}} \eta(t), \tag{7}$$

if the Eisenhart metric is used.

The instability growth rate of ψ measures the instability growth rate of $\|J\|^2$ (geodetic separation field) and thus provides the dynamical instability exponent in our Riemannian framework.

Equation (6) is a scalar equation that, independently of the knowledge of the dynamics, provides a measure of the average degree of instability of the dynamics itself through the behavior of $\psi(s)$. The peculiar properties of a given Hamiltonian system enter (6) through the global geometric properties $\langle k_R \rangle_\mu$ and $\langle \delta^2 K_R \rangle_\mu$ of the ambient Riemannian manifold whose geodesics are natural motions and are sufficient to determine the average degree of chaoticity of the dynamics.

3 Experimental results

In this section, we examine EEGs from an experimental murine model of human epilepsy that has seizures which like humans, are spontaneous, intermittent, and sometimes lethal. This mouse model was the product of genetic engineering in which the H218/AGR16/Edg-5/LP(B2) sphingosine 1-phosphate receptor gene has been disrupted. Beginning on postnatal day 19 through postnatal day 22, H218 deficient mice exhibit generalized seizures which can be easily identified in intracranial EEG recordings [8].

In brief, this experimental model was produced by knocking out the entire protein coding region of the single copy mouse H218 gene through homologous recombination [8]. Southern blot analysis with 3' and 5' probes, as well as PCR analysis confirmed the appropriate location of the mutation in both ES cells and mice following germ line transmission. The appearance and behavior of the newborn H218 gene deficient mice were indistinguishable from that of their control littermates. Postnatal days 19 through 22 H218 deficient mice ($n = 8$) were continuously monitored with video-EEG for electrographic and behavioral seizures. Microelectrodes were placed in both frontal and hippocampal regions, bilaterally (Fig. 1).

Signals were sampled at 200 Hz, using an analog to digital (A/D) converter with 12 bits quantitation, and amplifiers with input range of -2.5 to $+2.5$ mV and frequency range of 0.05 Hz to 70 Hz. These recordings were obtained using a BSMI/Nicolet (Madison, WI) 32 channel video-EEG instrument. Seizures consisted of wild-running fits and/or clonic-tonic movements of the arms and legs. Concomitant EEG changes consisted of continuous bilateral spike and wave discharges.

EEG seizures were the most robust over the frontal electrodes. Following each seizure, EEG background activity was slowed and suppressed by 50 % in comparison to the preictal EEG activity. At a cellular level, whole-cell patch clamp recordings revealed that the loss of H218 leads to a large increase in the excitability of neocortical pyramidal neurons [8]. The loss of H218 did not affect intrinsic membrane properties. However, the H218 neurons displayed significant increases in both the frequency and amplitude of spontaneous excitatory postsynaptic currents (sEPSCs). Under current clamp, spontaneous, paroxysmal depolarizing shift accompanied by bursts of action potentials were observed in 10 out of 14 H218 cells in physiological bath solution [8].

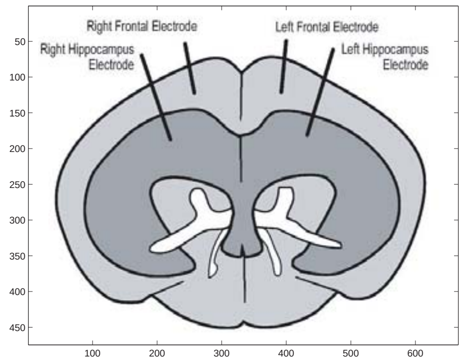

Figure 1. Schematic diagram of the depth electrode placement. Ictal discharge begins as spike and wave discharges in bilateral frontal and hippocampal electrodes.

Our experimental studies utilized the T-index of a homozygous and a wild mouse from an electrode site overlying the seizure focus (Figs. 2–6).

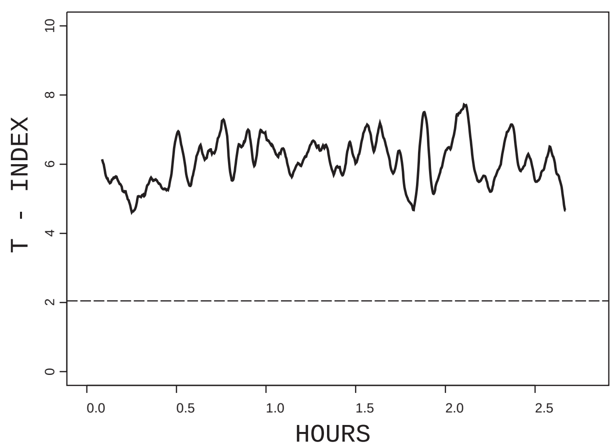

Figure 2. T-Index profiles in H218+/+ littermate. An example of continuous 3 hr trace obtained from a 21 day old littermate control illustrating a persistently higher average T-index. Note that the average T-index does not decline below the critical value of 2.045 (represented by the discontinuous horizontal line). No seizures occurred in littermates. T-index plot in postnatal day 21 control mouse.

Time-resolved analysis of intracranial electroencephalogram (EEG) signals recorded in a transgenic epileptic mouse indicates marked changes in spatiotemporal dynamics, often beginning several minutes prior to seizure onset. The spatiotemporal dynamics of this preictal (before seizure) transition differ markedly from that of the interictal (between seizure) period. If interpreted as a loss of complexity in the brain electrical activity of the mouse, these changes could reflect continuous increase synchronization between pathological discharging neurons and alow one to study seizures-generating mechanisms in a seizure-prone brain. Time-resolved analysis of neuronal activity recorded in a seizure prone mouse indicates marked changes in nonlinear dynamical characteristics for up to several minutes prior to seizure onset in comparison to the interictal seizure state.

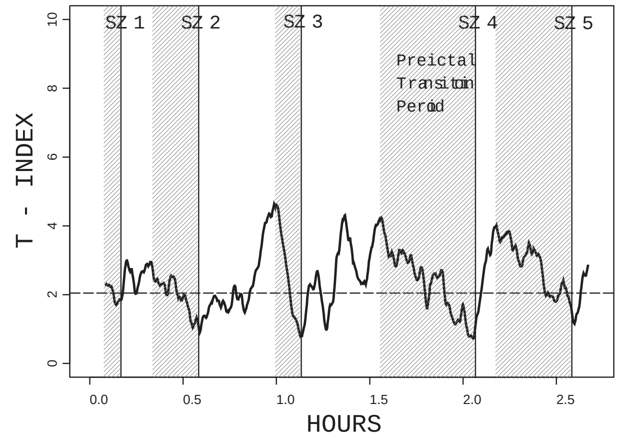

Figure 3. T-Index profiles in H218 deficient mice. Five seizures (SZ 1-5) are depicted during 3 hrs of continuous EEG recording in a 21 day old H218 deficient mouse. Lines indicate the time of the EEG seizure onset. The gray area represents the pre-seizure time period. Note that the average T-index falls below the threshold value of 2.045 several min prior to an EEG seizure.

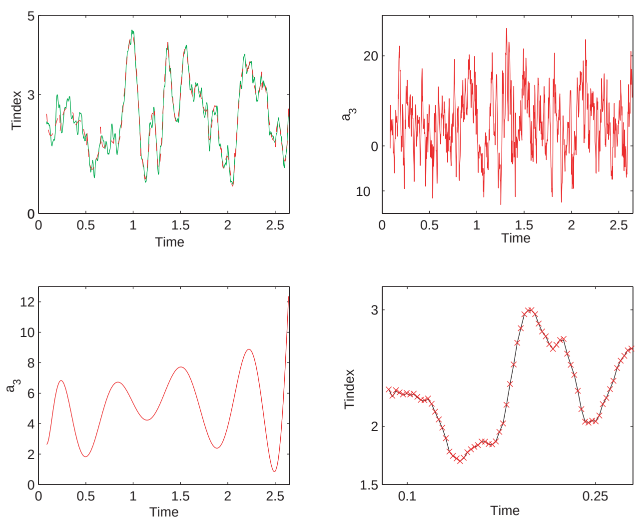

Figure 4. Local prediction T-index based on reconstructed three-dimensional model. The top two plots illustrate the T-index created from the H218 deficient mice and the corresponding parameter a_3 as function of time; the bottom two plots demonstrate the polynomial approximation of the parameter a_3 and estimated and predicted (criss-cross) T-index.

4 Conclusion

We have proposed a geometric approach to studying of the physiological disturbances that occur in human epilepsy. Under reasonable hypotheses, which obviously restrict the validity of the geometric approach, this paper provides the possibility for numerical computation of the state changes in the EEG signals using the largest Lyapunov exponent and the combination of the curvature of the underlying manifold and the geodesics. These geodesics flows may have very specific hidden symmetries, mathematically defined through Killing tensor field.

The development of an appropriate model of the epileptic brain will provide opportunities to investigate the effects of various approaches to a dynamical control. This would be an essential first step in the development of novel treatments, based upon the geometric theory of nonlinear dynamics. Clearly, further work is needed to carefully probe experimentally observed dynamics of the epileptic brain, and to clarify the bifurcation and self-organization structures that display complex probability distribution functions.

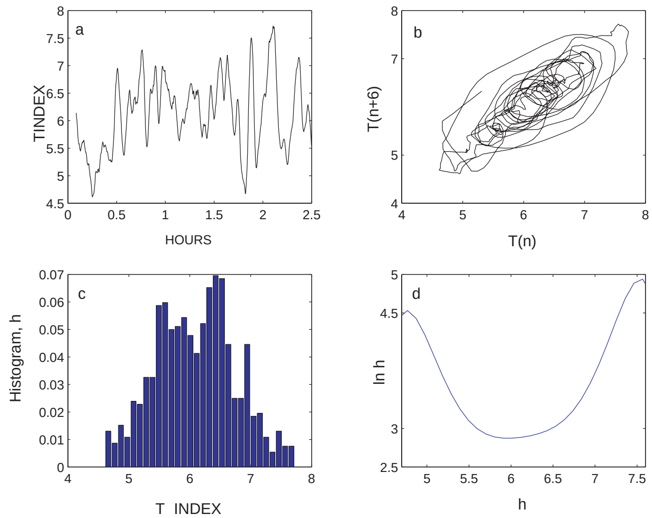

Figure 5. The top two plots illustrate the T-index created from the H218+/+ littermate deficient mice and the corresponding phase space; the bottom two plots demonstrate the histogram obtained from T-index and the and $\ln f$.

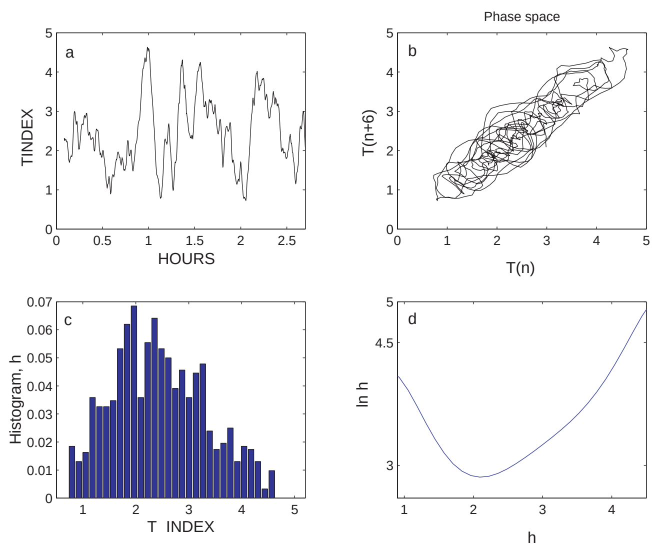

Figure 6. The top two plots illustrate the T-index created from the H218 deficient mice and the corresponding phase space; the bottom two plots demonstrate the histogram obtained from T-index and the and $\ln f$.

We estimate the T-index which reflects the complexity of the motion of the brain considered. Our results suggest that neuronal oscillatory behavior in the H218 deficient brain reflects neuronal network synchrony between frontal and hippocampal brain sites. Importantly, the observed oscillatory neuronal behavior occurs in anticipation of an impending seizure. The main factors that contribute to the occurrence of such synchronous oscillations in neuronal networks may include the intrinsic properties of the neurons, the structure of the interconnectivity between the networks elements, the synaptic processes that subserve specific inputs and feedback/feedforward loops, and the modulating influence from general or local neurotransmitters.

The hybrid time series analysis of ongoing EEG signals may be used to extract features of the signal which are characteristic of the preictal (before seizures) transition. It could be demonstrated that the synchronization phenomena of the preictal state differ clearly from that found during seizures-free interval under various conditions. Both synchronization duration and strength are of a sufficient magnitude to open a time frame that provides possibilities for pharmacological or electro-physiologic interventions in the pre-ictal period. It remains to be established whether different methods of nonlinear time series analysis can provide information that will lead to understanding of the mechanisms underlying epileptogenesis.

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[1] Brewis M., Poskanzer D.C., Rolland C. and Miller H., Neurological disease in an English city, *Acta Neurologica Scandinavica*, 1996, V.42, N 24, 9–89.

[2] Cockerell O.C., Eckle I, Goodridge D.M., Sander J.W. and Shorvon S.D., Epilepsy in a population of 6000 re-examined: secular trends in first attendance rates, prevalence, and prognosis, *J. Neurol. Neurosurg. Psychiatry*, 1995, V.58, N 5, 570–576.

[3] Jallon P., Epilepsy in developing countries, *Epilepsia*, 1997, V.38, N 10, 1143–1151.

[4] Elger C.E. and Lehnertz K., Seizure prediction by non-linear time series analysis of brain electrical activity, *European Journal of Neuroscience*, 1998, V.10, N 2, 786–789.

[5] Andrzejak R.G., Widman G., Lehnertz K., Rieke C., David P. and Elger C.E., The epileptic process as nonlinear deterministic dynamics in a stochastic environment: an evaluation on mesial temporal lobe epilepsy, *Epilepsy Research*, 2001, V.44, 129–140.

[6] Lehnertz K., Andrzejak R.G., Arnold J., Widman G., Burr W., David P. and Elger C.E. Possible clinical and research applications of nonlinear EEG analysis in humans, in Chaos in Brain, Editors K. Lehnertz, J. Arnold, P. Grassberger and C.E. Elger, London, World Scientific, 2000, 134–155.

[7] Iasemidis L.D., Shiau D.S., Pardalos P. and Sackellares J.C., Transition to epileptic seizures: optimization, in Discrete Problems with Medical Applications, Editors D.Z. Du, P. Pardalos and J. Wang, *DIMACS Series*, Vol. 55, American Mathematical Society, 2000, 55–74.

[8] MacLennan A.J., Carney R.P., Zhu W.J., Chaves A.H., Garcia J., Grimes J.R., Anderson K.J., Roper S.N. and Lee N., An essential role for the H218/AGR16/Edg-5/LP(B2) sphingosine 1-phosphate receptor in neuronal excitability, *Eur. J. Neurosci.*, 2001, V.14, 203–209.

[9] Abarbanel H., Analysis of observed chaotic data, New York, Springer-Verlag, 1995.

[10] Pardalos P., Sackellares J.C. and Yatsenko V., Classical and quantum controlled lattices: self-organization, optimization and biomedical applications, in Biocomputing, Editor P. Pardalos, Dordrecht–Boston–London, Kluwer Academic Publishers, 2002, 199–224.

[11] Oseledec V.I., A multiplicative ergodic theorem. Characteristic Ljapunov, exponents of dynamical systems, *Trudy Mosk. Mat. Obsc.*, 1968, V.19, 179–210 (in Russian).

[12] Kaplan J. and Yorke J., The onset of chaos in a fluid flow model of Lorentz, *Annals of N.Y. Academy of Sci.*, 1977, V.316, 400–407.

[13] Casetti L. and Pettini M., Analytic computation of the strong stochasticity threshold in Hamiltonian dynamics using Riemannian geometry, *Phys. Rev. E*, 1993, V.48, 4320–4332.

[14] Pesin Ya., Dimension theory in dynamical systems. Contemporary views and applications, *Chicago Lectures in Mathematics*, Chicago, The University of Chicago Press, 1997.