

USING HIGUCHI'S FRACTAL DIMENSION IN FINE ANALYSIS OF THE EFFECTS OF 2.7 MT AND 10 MT STATIC MAGNETIC FIELDS ON THE COMPLEX BURSTING ACTIVITY OF THE SNAIL BR NEURON

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Abstract - The components of complex bioelectrical activity – action potential (AP), interspike interval (ISI) and the quiet interburst interval (IBI), along with the effects of 2.7 mT and 10 mT static magnetic fields, were identified and examined in the spontaneously active Br neuron of the subesophageal ganglion complex of the garden snail *Helix pomatia* by fractal analysis using Higuchi's fractal dimension (FD). The normalized mean of the empirical FD distributions of bursting activity of the Br neuron were formed under different experimental conditions: before (Control), during (MF), and after exposure to the static magnetic field (AMF). Using the fractal analysis method for the first time, a separation of the AP, ISI and IBI components was successfully achieved. Our results show that fractal analysis with deconvolution of the normalized mean of the empirical FD distributions into Gaussian functions is a useful tool for revealing the effects of magnetic fields on the complexity of neuronal bioelectric activity and its AP, ISI and IBI components.

Key words: Higuchi fractal dimension, bursting activity, Br neuron, static magnetic field

INTRODUCTION

There are very few studies involving nonlinear analysis of spontaneously active neurons and their components of complex bioelectrical activity, especially considering the widely accepted fact that physiological signals generated by living organisms are non-stationary and nonlinear by their nature (Goldberger et al., 2002). In the past few decades, concepts and techniques of nonlinear dynamics have been applied in different areas of biomedical research, from molecular to ecosystem level (Goldberger, 2001; Goldberger et al., 2002). It is of great importance that nonlinear signal analysis techniques such as the Higuchi fractal dimension, in addition to the classical linear ap-

proaches to signal analysis, is used in the monitoring of normal and altered physiological states. Higuchi's fractal dimension alone or in combination with other signal analysis techniques is very useful in the analysis of normal and altered bioelectric activities of single neurons and complex EEG signals in different experimental conditions. Thus, Higuchi's fractal dimension has been usefully applied in exploring the effect of the magnetic field on the activity of a single neuron (Spasić et al., 2011c, d), while complex EEG signals that originate from neuronal networks were examined during anesthesia (Klonowski et al., 2006; Spasić et al., 2011a, b), in an animal model of neurodegenerative disease caused by aluminum intoxication (Keković et al., 2010) and during brain injury

(Spasić et al., 2005; 2008; Spasić, 2010).

Bursting activity is one of the most easily recognizable types of neuronal bioelectric activities. This specific type of spontaneous neuronal spiking has been suggested to play a crucial role in many systems. Bursting bioelectric activity in the nervous system of invertebrates and vertebrates is associated with some of the most important physiological functions, such as respiration (Pena, 2008) and heartbeat (Levy et al., 1981). In the nervous systems of mammals, bursting neurons can be found throughout the neocortex (Le Bon-Jego and Yuste, 2007), thalamus (Bal and McCormic, 1993; Fuentealba and Steriade, 2005), cerebellum (Raman et al., 2000) and neuroendocrine cells (Stojilković, 2006). Bursting bioelectric activity consists of bursts of action potentials (AP) and interposed silent interburst periods (IBI) (Marsat et al., 2012). Bursts consist of trains of AP occurring in quick succession. The APs within the bursts are separated by interspike intervals (ISI). The generation of bursts in neurons might arise from strong synaptic inputs. In many cases, however, bursts are generated by the specialized intrinsic conductance of the neuron (Lisman, 1997). In the central nervous system of mammals, some neurons, such as cortical and thalamic, possess the ability to generate spontaneous activity with or without the presence of synaptic inputs (Dehaene and Changeux, 2005; Fuentealba and Steriade, 2005). Bursts of AP have a special role in neuronal signaling. Thus, APs that are generated in bursts provide more accurate information than those that arrive singly (Lisman, 1997).

Having in mind the important role of bursting neurons in the nervous system of both invertebrates and vertebrates, it is very important to examine the changes in the bioelectric properties of these neurons in response to external stimuli. Previous research showed that magnetic field could tune the spiking pattern of bursting activity of the Br neuron in the snail nervous system (Nikolić et al., 2008; 2012). Furthermore, previous research showed that bursts of AP could be shaped by exposing the Br neuron to 2.7 or 10 mT magnetic fields for 15 min (Nikolić et al., 2008). In this study, we used a different experimental

approach: we examined the effects of 2.7 mT and 10 mT static magnetic fields on the bursting complexity of the Br neuron in the subesophageal ganglia of the garden snail *Helix pomatia* using Higuchi's fractal dimension.

In the present study, we tried to separate and numerically define each component (AP, ISI and IBI) of bursting activity of Br neuron with the normalized mean of group empirical distribution of fractal dimension (*FD*) and Gauss fitting procedure. Secondly, we used this approach to investigate the effects of moderate intensity static magnetic fields (2.7 mT and 10 mT) on the bursting complexity of the Br neuron. Thirdly, we examined the comparative effect of these magnetic fields on the complexity of Br neuron activity.

MATERIALS AND METHODS

Experimental procedure, data recording and acquisition

All experiments were performed on the Br neuron in the isolated subesophageal ganglion complex of *Helix pomatia* (*Pulmonata: Helicidae*), positioned in the lower part of the right parietal ganglion (Nikolić et al., 2008). The permanent magnets, which produced static magnetic fields of 2.7 mT and 10 mT, were placed on a custom-made holder below the center of the recording chamber, with the North Pole parallel to the vertical component of the geomagnetic field, at approximately 3 mm from the bottom of the chamber. The value of the local geomagnetic field (44°38'N, 20°46'E), measured by a GSM 10 proton magnetometer in the Geomagnetic Observatory, Belgrade, throughout the experiments was 47.51 μ T. We have already proved a consistency of the magnetic field induction on the small dimension of the experimental object, with an average induction of 2.71 ± 0.03 mT and 10.00 ± 0.21 mT in the recording chamber (Nikolić et al., 2008; 2012; Spasić et al., 2011c). The electrophysiological recordings of Br neuron activity were performed before, during and after exposure to the static magnetic fields of 2.7 mT ($n=6$) and 10 mT ($n=5$) for 15 min, according to the

procedure thoroughly described in Nikolić et al. (2008). For the fractal analysis, we used only the first 5 min epochs of each experimental condition: before (Control), during exposure to the static magnetic field (MF), and after exposure to the static magnetic field (AMF).

Higuchi's fractal dimension and fractal analysis

Higuchi's fractal dimension is used as a nonlinear measure of signal complexity in the time domain (Higuchi, 1988). Fractal analysis was performed by an FD calculating of electrophysiological signals from Br neurons using Higuchi's method. It has proved to be a useful in characterizing signal properties, and a simple and fast computational tool for the assessment of signal nonlinearity (Accardo et al., 1997; Spasić et al., 2008; Raghavendra and Narayana Dutt, 2010; Spasić, 2010). This fractal analysis method, usually applied to stationary signals, was modified (Spasić et al., 2011c, d) for the analysis of highly non-stationary signals – the bimodal pattern of single neuron activity. We applied Higuchi's algorithm using a self-made program in MATLAB 6.5 software. The procedure with a full method description has already been given in our previous papers (Spasić et al., 2008; 2011c, d; Spasić, 2010).

We chose the parameter $N=25$ equivalent to an epoch of 0.025 s duration to deal with non-stationary signals, and the parameter $k_{\max} = 8$. Signals were divided into 12 000 epochs (windows) and FD values were calculated for each epoch, without overlap. The theoretical values of FD should be in the interval [1, 2]. However, in practice Higuchi's fractal dimension may lie slightly outside the [1, 2] range, because it is only an estimate by a numerical method. In order to facilitate the interpretation of FD values, we could say that FD is related to the "geometrical" complexity of the curves. The FD value of smooth curves was estimated to be approximately 1, and from the other side the FD of random white noise was estimated to be approximately 2. In addition, we can say that the increase in signal frequency is directly proportional to the increase in FD . Therefore, we will show that the FD values of bursting periods should be ~ 1 on

average; the interspike periods should be characterized by $FD \sim 1.5$ on average; the FD values of silent periods should be >1.8 on average. It should be mentioned that in our previous study we characterized the frequency of AP, ISI, and IBI as a number of their appearances observed in a certain period of time. However, to avoid misunderstandings, in this work the frequency of AP, ISI, and IBI is observed as the content of their geometrical complexity. Thus, in the present work frequency will be considered only in this context.

FD values were calculated for signals recorded before, during and after exposure to the static magnetic fields of 2.7 mT (total 18 signals, 6 signals per condition) and 10 mT (total 15 signals, 5 signals per condition). The empirical FD distributions of each separate signal were formed and the mean of empirical FD distributions of Br neuron activity in each experimental condition – before (Control), during (MF), and after exposure to the static magnetic field (AMF), were calculated. Additionally, normalization of mean empirical FD distribution was performed by dividing the frequencies for each group with its sum value. In order to establish concrete boundaries between AP, ISI, and IBI components in the signal, a MATLAB user-defined peak fit function was used. We fit peaks in the empirical FD distribution with a Gaussian model and isolated three Gaussian peaks in every signal separately. A fit with three peaks yields very good results with small errors. Peak positions give us the mean FD values of each (AP, ISI, and IBI) component in the signal and could help to define boundaries between them. Thereafter, we calculated areas under the curves, limited by the boundaries of AP, ISI, and IBI components, for each experimental condition, using cumulative distribution function (CDF).

Statistical analysis

Using the nonparametric Kolmogorov-Smirnov Test for two independent samples (using SPSS 13.0 software), the differences between the normalized values of the mean empirical FD distribution obtained before, during and after exposure to the static magnetic

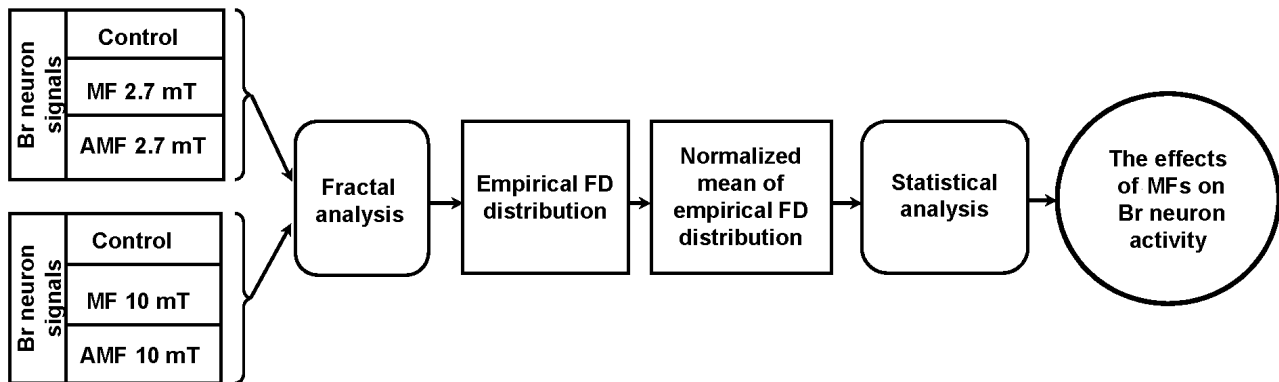


Fig. 1. A schematic overview of applied signal processing model.

fields of 2.7 mT and 10 mT were tested within and between the exposed groups. A schematic overview of the applied signal processing that led to the results in this paper is given in Fig. 1.

RESULTS

In order to determine precisely the changes in the complexity of bursting activity of the Br neuron caused by 2.7 mT and 10 mT static magnetic fields, we needed to accurately define AP, ISI, and IBI by using empirical distributions of Higuchi's FD and their deconvolution into Gaussians. A typical individual example (60 s epoch) of bursting activity of the Br neuron in a control condition, corresponding fractal dimension values and isolated three Gaussian peaks in normalized empirical FD distribution corresponding to AP, ISI, and IBI components, respectively, are presented in Fig. 2A. As we showed in Spasić et al. (2011c), FD values <1.2 characterize the periods of bursting action potentials of tested Br neurons. To separate the AP and ISI components we used the intersection of two Gaussian fitting lines at the $FD = 1.3$. After the deconvolution into Gaussians of all separate signals, we determined the following limits: FD values in the interval of $[0.9, 1.3]$ characterize the AP, FD values in the intervals of $[1.3, 1.75]$ originate from the ISI and FD values in the interval of $[1.75, 2.2]$ originate from silent IBI. To be certain that we had properly differentiated the AP, ISI, and IBI components of the Br neuron, we separately analyzed the

bioelectric activity of Br neuron characterized by the existence of AP and ISI without IBI (Fig. 2B). In this condition, we could isolate only two Gaussian peaks in normalized empirical FD distribution, with the first peak position at $FD = 1.205$ and $FD = 1.504$ for the second (Fig. 2B). This condition has been very useful in assigning the FD interval values related to the IBI component. As there were no IBIs in the signal, there was no peak at the empirical FD distribution function. Hence, it could be seen that the lower boundary for the IBI is between 1.7 and 1.8. After we had accurately determined the AP, ISI, and IBI components of the bursting activity of Br neuron, we were able to analyze the effects of 2.7 mT and 10 mT static magnetic fields on the fractal dimension values of each of these parameters. In addition, the empirical FD distributions for each separate signal and mean group empirical FD distributions are formed and normalized. After a normalized mean of the empirical FD distribution was formed, we calculated CDF for all experimental conditions in order to define numerically the area under the curves.

Statistical tests and the cumulative distribution function within the exposed groups showed that exposure to 2.7 mT and 10 mT static magnetic fields induced changes in the complexity of bursting activity of snail Br neuron. Our data showed that both magnetic fields influenced the complexity of the Br neuron burst period (AP with ISI) compared with control conditions (Fig. 3A, B; Tables 1, 2, 3). The

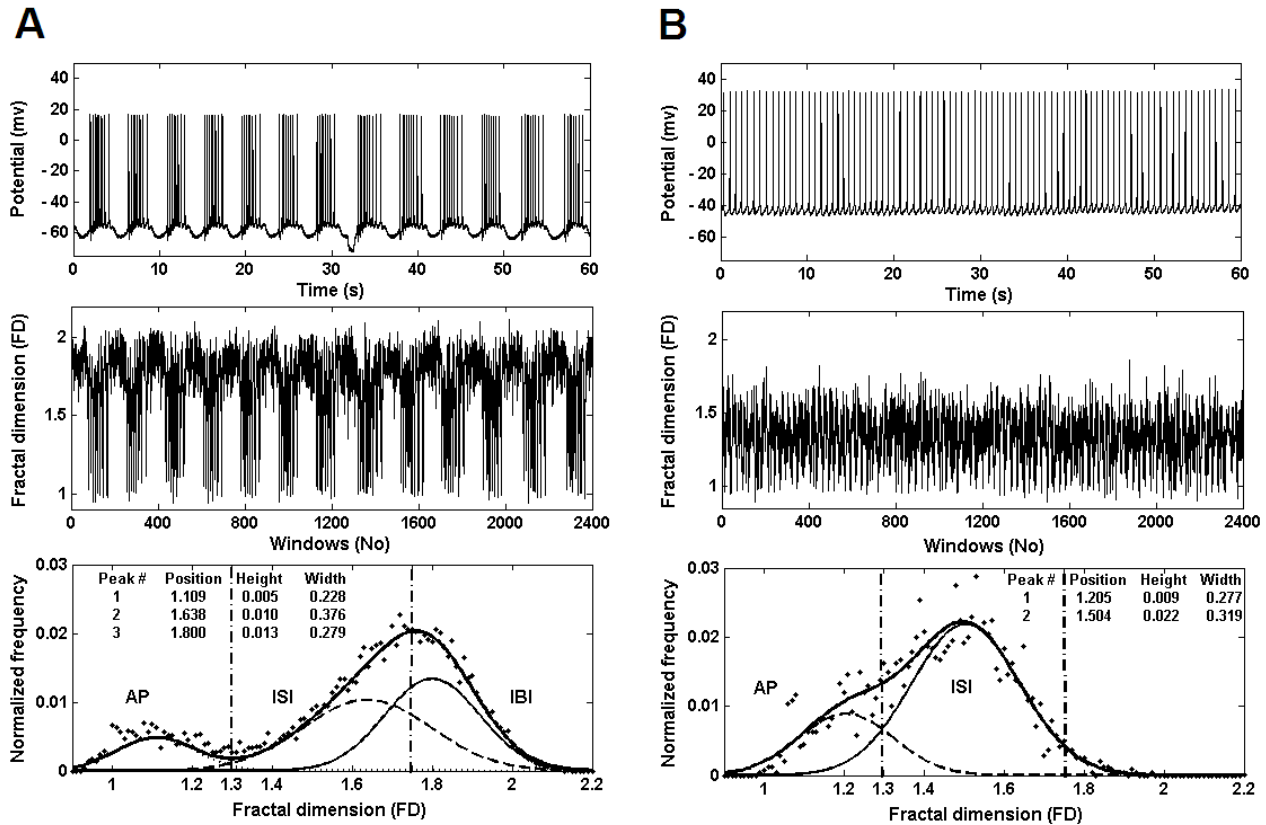


Fig. 2. (A) Typical bursting activity of the Br neuron (60 s epoch) in control condition, corresponding fractal dimension values in time domain, and normalized empirical *FD* distribution (lower panels) and (B) electrophysiological activity of the Br neuron (60 s epoch) under control condition without an interburst period, corresponding fractal dimension values in time domain, and normalized empirical *FD* distribution (lower panels). Isolated Gaussian peaks (peak position, height and width) in the normalized empirical *FD* distribution with Gaussian model fitting (lower panels).

weaker 2.7 mT magnetic field induced changes in the complexity of the ISI component of the burst period of Br neuron activity. Furthermore, the normalized mean of the empirical *FD* distribution showed that exposure to 2.7-mT magnetic field significantly increased the participation of ISI in comparison to control conditions (Fig. 3A; Tables 1, 2, 3). The stronger 10-mT magnetic field exerted its effect on the burst period by significantly changing the complexity of the AP component (Fig. 3B; Tables 1, 2, 3). Obtained data showed that the examined magnetic fields did not significantly change the complexity of the IBI component in the bursting activity of Br neuron. In addition, our results showed that the effects of 2.7 mT and 10 mT magnetic fields on the complex-

ity of bursting activity of the Br neuron are persistent and visible in the AMF period. Specifically, it can be seen that both magnetic fields induced significant changes in the participation of the AP component in the mean of normalized empirical *FD* distribution (Fig. 3A, B; Tables 1, 2, 3). By comparing the mean of empirical *FD* distributions between 2.7 mT and 10 mT magnetic fields, we observed the same trend of changes in the AP interval, as well as differences in the complexities of ISI and IBI components during exposure to the magnetic fields (Fig. 3C; Tables 1, 2, 3). Compared to 2.7 mT, the stronger 10-mT magnetic field significantly reduced participation of the ISI component and increased participation of the IBI component in the mean of normalized empirical

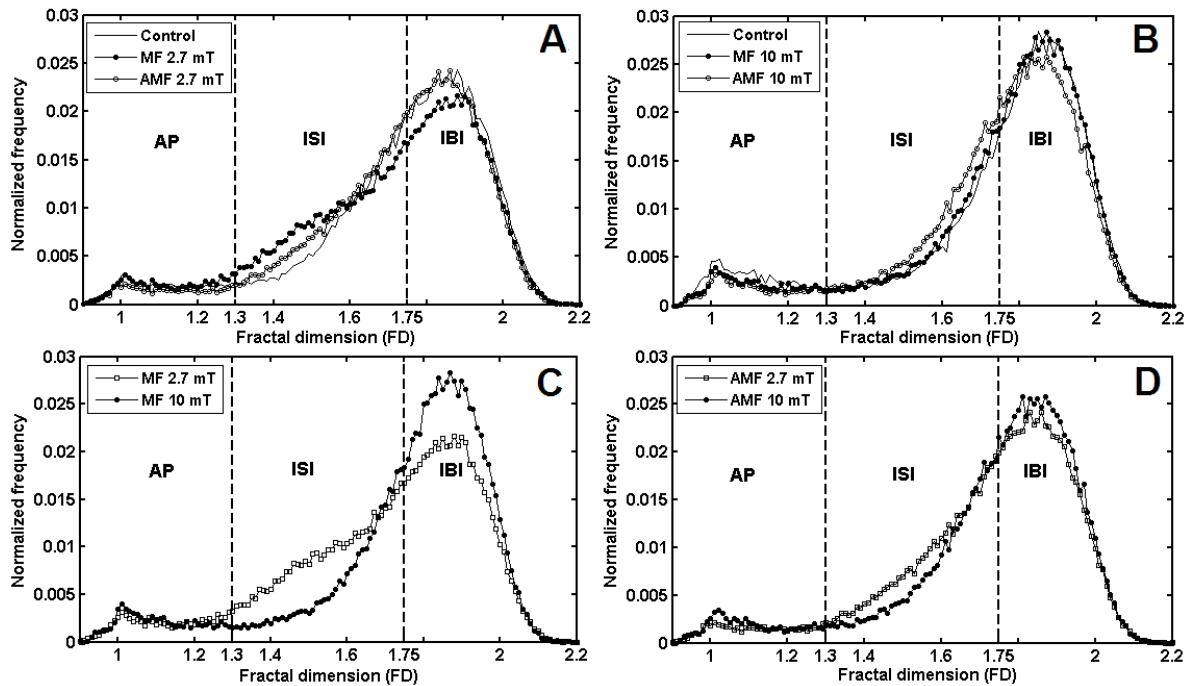


Fig. 3. (A) Normalized group mean of the empirical *FD* distributions in control, during (MF) and after exposure (AMF) to 2.7 mT static magnetic field for six snails, and (B) under control, during (MF) and after exposure (AMF) to 10 mT static magnetic field for five snails. (C) Comparison between normalized group mean of the empirical *FD* distributions during exposure to static magnetic fields of 2.7 mT and 10 mT, and (D) after exposure to the same static magnetic fields.

FD distribution. After exposure to magnetic fields, changes in all components followed the same trend but were less pronounced (Fig. 3D; Tables 1, 2, 3).

DISCUSSION

Invertebrate neurons have proved to be good model system for understanding how the central nervous system (CNS) of vertebrates works in normal and altered states, because they are accessible for experimentation and investigation of the basic mechanism underlying neural excitability (Lewis et al., 1986). The Br neuron of snail subesophageal ganglion complex is large (200–500 μm), with a constant position on the surface of the ganglia and consistent type of synaptic connections. The Br neuron rhythmically generates regular bursts of AP with silent IBI periods (Vadasz and Salanki, 1976; Kononenko, 2000), and is involved in neuronal regulation of various homeostatic and adaptive mechanisms (Jahan-Parwaret et

al., 1969; Rittenhouse and Price 1985; Alevizos et al., 1991).

Mechanisms that establish and maintain spontaneous bioelectrical activity of snail neurons are similar to those that can be found in the CNS of vertebrates and humans, pointing to the importance of our research. Spontaneous neuronal activities in several neural regions have been conserved among invertebrates and vertebrates species (Yamamoto and López-Bendito, 2012) and are a property of many developing neural circuits, including the retina, cochlea, spinal cord, cerebellum and hippocampus, with a crucial role in establishing connections among neurons (Blankenship et al., 2010). Electrophysiological mechanisms that generate and modulate burst firing in invertebrates are present in CNS neurons of mammals and may participate in abnormal rhythmical activity, which could lead to the emergence of epilepsy (Lewis et al., 1986; McCormick, 2002).

Table 1. Results of the Kolmogorov-Smirnov test for two independent samples. Bold p-values are significant

Within groups	2.7 mT			10 mT		
	AP	ISI	IBI	AP	ISI	IBI
Control vs. MF	$p = 0.28$	$p = 0.03$	$p = 0.14$	$p = 0.02$	$p = 0.65$	$p > 0.99$
Control vs. AMF	$p < 10^{-4}$	$p = 0.48$	$p > 0.99$	$p < 10^{-4}$	$p = 0.48$	$p = 0.33$
MF vs. AMF	$p < 10^{-4}$	$p = 0.48$	$p = 0.08$	$p = 0.28$	$p = 0.65$	$p = 0.22$
Between groups	AP	ISI	IBI			
MF - 2.7 mT vs. 10 mT	$p = 0.59$	$p < 10^{-4}$	$p < 10^{-3}$			
AMF - 2.7 mT vs. 10 mT	$p = 0.17$	$p = 0.22$	$p = 0.22$			

Table 2: Proportional participations (%) of AP, ISI, IBI in normalized group mean of the empirical FD distribution before (Control), during (MF) and after exposure (AMF) to 2.7 mT and 10 mT static magnetic fields.

	2.7 mT			10 mT		
	AP	ISI	IBI	AP	ISI	IBI
Control	7.33 %	36.78 %	55.89 %	10.29 %	27.09 %	62.62 %
MF	7.84 %	41.94 %	50.22 %	7.82 %	29.13 %	63.05 %
AMF	5.70 %	40.92 %	53.38 %	6.79 %	35.21 %	58.00 %

Table 3. Differences in participation (%) of AP, ISI, IBI in normalized group mean of the empirical FD distribution before (Control), during (MF) and after exposure (AMF) to 2.7 mT and 10 mT static magnetic fields.

	2.7 mT			10 mT		
	AP	ISI	IBI	AP	ISI	IBI
Control - MF	-0.51 %	-5.16 %	5.67 %	2.47 %	-2.04 %	-0.43 %
Control - AMF	1.63 %	-4.14 %	2.51 %	3.50 %	-8.12 %	4.62 %
MF - AMF	2.14 %	1.02 %	-3.16 %	1.03 %	-6.08 %	5.05 %

In the present work, using a normalized mean of the empirical distributions of fractal dimension values and their deconvolutions with Gaussian model peak fitting, we succeeded in differentiating AP, ISI, and IBI components of spontaneous Br neuron activity. In our previous work (Spasić et al., 2011c), we could define only spiking and interbursting activity. As far as we know, this is the first successful application of Higuchi's fractal dimension as a method for separating the various components (AP, ISI, and IBI) of complex bioelectrical activity. Therefore, it is a methodological contribution complementary to conventional analysis of bursting activity, allowing fast computational tracking of variations in signals (Raghavendra and Narayana - Dutt, 2010). Calculation of FD by Higuchi's algorithm is fast and simple and it has often been used in combination with other

methods such as pattern entropy in revealing the influence of magnetic fields on the EEG patterns of human brain (Klonowski et al., 2000).

Linear methods for signal analysis like FFT (Fast Fourier Transform) and WT (wavelet transform) work properly only for stationary signals, while for the Higuchi fractal dimension it does not matter if the analyzed signal is non-stationary, deterministic or stochastic (Klonowski, 2009; Spasić et al., 2008; 2011c). Processes within snail (*Helix pomatia*) spontaneously active central ganglia induced by odor inputs are time-evolving (non-stationary) (Schütt et al., 2002), as are brain electrical signals from behaving or sleeping crayfish (Mendoza-Angeles et al., 2007). In addition, the nonlinearity of individual neuronal activity is a widely accepted fact (Rabinovich and

Abarbanel, 1998). Thus, the application of Higuchi's fractal dimension for the quantification of dynamically evolving neuronal electrical activity like those from our experiments has advantages in comparison to FFT or WT approaches, especially if we do not know the true nature of recorded signals. By implementing this methodology we were able to investigate the effects of moderate intensity magnetic fields (2.7 mT and 10 mT) on the complexity of bursting activity of snail Br neuron, and further to examine the comparative effect of these magnetic fields on the complexity of the Br neuron activity.

In the present work, using fractal analysis we showed that the investigated moderate-intensity magnetic fields of 2.7 mT and 10 mT induced changes in the complexity of bursting activity of the Br neuron. In our previous studies (Spasić et al., 2011c, d), we used independent component analysis (ICA) and factor analysis as useful tools for the identification of the impact of a 2.7 mT static magnetic field on snail bursting activity. In this paper, we have shown that fractal analysis with deconvolution of the normalized empirical *FD* distributions into Gaussian functions is a useful tool in monitoring the effects of magnetic fields on neuronal bursting activity, especially in AP, ISI, and IBI components separately. As our previous and other studies suggest, a magnetic field of several mT can have direct effects on neurons and other non-neural cells, resulting in changes in membrane properties and neuronal functioning (Fuller et al., 1995; McLean et al., 1995; Todorović et al., 2007; Ye et al., 2004; 2008; Nikolić et al., 2008; 2012).

We propose that Higuchi's fractal dimension measure be adopted for further studies of spontaneous active neurons in vertebrates, such as thalamic reticular nucleus neurons, cerebellar nuclei neurons, and neocortex neurons, *in vivo* and *in vitro*. In the context of the effects of the investigated magnetic fields on snail Br neurons, we can assume that similar changes in bursting activity can occur in spontaneously active neurons in vertebrates exposed to a magnetic field. Azanza and Calvo, (2000) have already proved that the behavior of the single neuron

in the snail (*Helix aspera*) under exposure to static (3 mT-0.7 T) and alternating (1-15 mT) magnetic fields fits well with the electrophysiological activity described for mammals and human whole brain under magnetic stimulation (pulsed magnetic field range: 0.3 mT-2.4 T).

Future studies using fractal analysis, ICA and other mathematical analyses should reveal the possible effects of stronger magnetic fields. The methodological approaches for signal analysis presented in this paper can provide further information on the effects of magnetic fields on human and animal health in order to fill the gaps in our knowledge. Generally, Higuchi's fractal dimension may be a very useful measure in combination with other techniques for single and assembly neuron activity analysis, in normal and altered physiological states.

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