Original article

Bifurcation analysis of the Poincaré map function of intracranial EEG signals in temporal lobe epilepsy patients

Mahmood Amiri\textsuperscript{a}, Esmaeil Davoodi-Bojd\textsuperscript{a}, Fariba Bahrami\textsuperscript{b}, Mohsin Raza\textsuperscript{c,}\textsuperscript{*}

\textsuperscript{a} School of Electrical and Computer Engineering, College of Engineering, University of Tehran, Tehran, IR Iran
\textsuperscript{b} CIPCE, School of Electrical and Computer Engineering, College of Engineering, University of Tehran, Tehran, IR Iran
\textsuperscript{c} Section of Neurosciences and Ethics, Chemical Injuries Research Centre, Baqiyatallah University of Medical Sciences, Tehran, IR Iran

Received 20 December 2009; received in revised form 23 February 2011; accepted 24 March 2011
Available online 13 April 2011

Abstract

In this paper, the Poincaré map function as a one-dimensional first-return map is obtained by approximating the scatter plots of inter-peak interval (IPI) during preictal and postictal periods from invasive EEG recordings of nine patients suffering from medically intractable focal epilepsy. Evolutionary Algorithm (EA) is utilized for parameter estimation of the Poincaré map. Bifurcation analyses of the iterated map reveal that as the neuronal activity progresses from preictal state toward the ictal event, the parameter values of the Poincaré map move toward the bifurcation points. However, following the seizure occurrence and in the postictal period, these parameter values move away from the bifurcation points. Both flip and fold bifurcations are analyzed and it is demonstrated that in some cases the flip bifurcation and in other cases the fold bifurcation are the dynamical regime underlying epileptiform events. This information can offer insights into the dynamical nature and variability of the brain signals and consequently could help to predict and control seizure events.

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Keywords: Poincaré map; Bifurcation analysis; Epilepsy; Evolutionary algorithm

1. Introduction

The brain is a complex network of interacting subsystems and it is now well documented that synchronization plays an important role in normal and abnormal brain functioning. A well-known case for pathophysiologic neuronal synchronization is epilepsy [2,20]. Epilepsy is a common neurological disorder, second only to stroke, that affects more than 50 million people worldwide. It is characterized by recurrent seizures or ictal events and impairs normal functions of the brain. These seizures are signs of excessive synchronous neuronal activity in the brain [1,11]. Two-thirds of the patients achieve sufficient seizure control from anticonvulsive drugs and about 8–10% could benefit from resective surgery. For the remaining of patients, no satisfactory treatment is currently available [24].

\textsuperscript{*} Corresponding author.
E-mail address: mohsimeza60@yahoo.com (M. Raza).
The neurophysiologic signals such as electroencephalograph (EEG) that reflect the macroscopic spatio-temporal dynamics of the brain activity have received worthwhile attention in recent years [5]. Since EEG signal can be considered as the output of a highly nonlinear and multidimensional dynamic system, the framework of nonlinear dynamical systems provides new concepts and powerful tools in order to extract relevant information from EEG signals [37]. Several studies indicate that nonlinear methods can extract valuable information from neuronal dynamics [5]. Currently, epilepsy is probably the most important application for nonlinear EEG analysis [34]. Babloyantz and Destexhe were among the first to apply nonlinear dynamics to analyze absence seizure (3 Hz spike and wave discharges) [6]. The correlation dimension of this type of seizure was lower than the dimension of normal waking EEG. This suggested that epileptic seizures might be due to a pathological ‘loss of complexity’. In the same way, Iasemidis and his colleagues showed the decrease of the largest Lyapunov exponent for patients with temporal lobe epilepsy. They found that the EEG activity progressively becomes less chaotic as the seizure approaches [14,15]. Since these pioneering studies, nonlinear dynamical system theory has been employed to quantify the changes in the brain dynamics in preictal, ictal and postictal periods. Other studies based on nonlinear associations in multivariate signals have reported that long distance functional connectivity is considerably changed during seizures [13] or indicated that the topology of networks alters as ictal activity grows [7,30].

The fact that the interictal EEG is high dimensional and seizure activity is low dimensional, raises the question as to how the transition between these two states can occur. This transition has two aspects: changes in the local dynamics of attractors and changes in the coupling between different brain areas [21,34]. With respect to the second aspect, seizures are generally characterized by an increase in coupling among different brain areas. However, in some types of seizures, there is a decrease in the level of coupling [9,25]. Regarding the first aspect, Lopes da Silva and his collaborators reviewed the dynamics of seizure generation. They proposed three different routes to epileptic seizures: (1) an abrupt transition, of the bifurcation type; this would be characteristic of absence seizure; (2) reflex epilepsy: deformation of the attractor is caused by an external stimulus and (3) a deformation of the attractor leading to a gradual evolution onto the ictal state (temporal lobe epilepsy) [21,34]. Therefore, the theory of nonlinear dynamical systems suggests that the state transition is probably due to arising of one or more bifurcations when some critical parameters of a neuronal network change.

When studying a highly complex system, a conventional approach is to reduce the system’s multidimensional continuous trajectory in the state space to a discrete low dimensional projection which is known as Poincaré map [33]. The question of how to determine the specific dynamical regimes of brain activity has caught considerable attention among neurophysiology and engineering communities. In this respect, Velazquez and his colleagues constructed a return map and qualitatively analyzed the dynamical regimes underlying epileptiform events [28,29]. The main concept of their studies was to use the time interval between spikes in EEG recordings as a variable to construct inter-peak interval (IPI) plots. In this way, neuronal population activity during the transition to seizure as well as during seizures could be studied. For approximating the local system dynamics, a first-return one dimensional mapping function was obtained by a Levenberg–Marquardt (LM) fitting of the IPI plot with an inverted polynomial. It should be pointed out that this mapping function is not an accurate model of epileptic activity and cannot reveal the rich variety of brain dynamics. However, it can characterize the state of the system by capturing essential phenomena of the collective dynamics of brain network and provides a relatively good approximation to the dynamics observed [18,26].

Drawing on these concepts, in this paper a quantitative analysis of some important dynamical mechanisms that may take place during epileptic neuronal activity is presented. Similar to the procedure that was used by Velazquez and colleagues, a first-return one dimensional map (Poincaré map) is obtained by approximating the scatter plots of IPI during preictal, ictal and postictal periods. For doing so, invasive EEG recordings of nine patients suffering from medically intractable focal epilepsy are used. In this way, a discrete representation of the original time series is provided. Evolutionary Algorithm (EA) is utilized for parameter estimation of the Poincaré map. Mathematical analyses reveal that the flip and fold bifurcations can occur during the transition to seizure.

The outline of the paper is as follows: in Section 2, some relevant definitions and theorems will be introduced and then the intracranial EEG data recorded at the Epilepsy Center of the University Hospital of Freiburg, Germany are explained. The construction process of the first-return IPI scatter plots and its approximation by an inverted quadratic polynomial are also covered in this section. In Section 3, based on the bifurcation theory, some explicit equations are derived which relate the bifurcation types to the Poincaré map parameter values. The results of some simulation are discussed in Section 4 and finally, Section 5 concludes the paper.
2. Materials and methods

2.1. Preliminary remarks

Dynamical systems may be continuous or discrete, depending on whether they are described by differential or difference equations. The difference equation for a general time-invariant discrete dynamical system can be written as:

\[ X_{k+1} = f(X_k) \quad k = 0, 1, \ldots \]  

where \( f : \mathbb{R}^n \rightarrow \mathbb{R}^n \), \( X \in \mathbb{R}^n \) can be a linear or nonlinear function of \( X_k \) [3]. The following definitions and theorems are of interest in (1) [4,19]:

**Definition 1.** A point \( \bar{x} \in \mathbb{R} \) is an equilibrium point for the dynamical system (1), or a fixed point for map \( f \), if \( f(\bar{x}) = \bar{x} \).

**Definition 2.a.** A fixed point \( \bar{x} \) of (1) is said to be stable if for any \( \varepsilon > 0 \) there exists \( \delta > 0 \) such that whenever \( |x_0 - \bar{x}| < \delta \), the point \( \bar{x} \) satisfies \( |x_k - \bar{x}| < \varepsilon \).

**Definition 2.b.** A fixed point \( \bar{x} \) of (1) is said to be unstable if it is not stable.

**Definition 2.c.** A fixed point \( \bar{x} \) of (1) is said to be asymptotically stable or an attracting fixed point of the function \( f \) if it is stable and, in addition, there exists \( r > 0 \) such that for all \( x_0 \) satisfying \( |x_0 - \bar{x}| < r \), then sequence \( x_k \) satisfy \( \lim_{k \to \infty} x_k = \bar{x} \).

**Definition 3.** Let \( A \) denote the Jacobian matrix \( \partial f/\partial x \) evaluated at \( \bar{x} \). The Eigen-values \( \mu_1, \mu_2, \ldots, \mu_n \) of \( A \) are called multiplier of the fixed point. A fixed point is called a hyperbolic if there are no multipliers on the unit circle (if \( |\mu| \neq 1 \)).

**Definition 4.a.** The bifurcation associated with the appearance of \( \mu = 1 \) is called a fold, tangent or saddle-node bifurcation.

**Definition 4.b.** The bifurcation associated with the appearance of \( \mu = -1 \) is called a flip or period doubling bifurcation.

**Theorem 1.** Let \( f : \mathbb{R} \rightarrow \mathbb{R} \) be continuously differentiable in a neighborhood of \( \bar{x} \), then \( \bar{x} \) is asymptotically stable if \( |f'(\bar{x})| < 1 \) and is unstable if \( |f'(\bar{x})| > 1 \).

2.2. EEG data

The data used in this study are EEG data from epileptic subjects made available online at \(<http://epilepsy.uni-freiburg.de/freiburg-seizure-prediction-project/eeg-database>\). The EEG database contains invasive EEG recordings of 21 patients, suffering from medically intractable focal epilepsy with a total of 88 seizures, 509 h of interictal, and 73 h of preictal or ictal EEG data. The interictal periods were at least 1 h distant to any seizure. Between two and five seizures (mean 4.2) per patient were examined, each with a seizure-free preictal phase of 50 min [23]. In this study, we used invasive EEG recordings of nine patients suffering from temporal lobe epilepsy. The data were recorded during invasive pre-surgical epilepsy monitoring at the Epilepsy Center of the University Hospital of Freiburg, Germany. In order to obtain a high signal-to-noise ratio, fewer artifacts, and to record directly from focal areas, intracranial grid-, strip-, and depth-electrodes were utilized. The EEG data were acquired using a Neurofile NT digital video EEG system with 128 channels, 256 Hz sampling rate, and a 16 bit analog-to-digital converter. Possible line noise was eliminated with a 50-Hz notch filter. Further details for data acquisition and patient characteristics are presented in the website or can be found in [23]. Fig. 1 shows the EEG signal for patient number two.
2.3. Computing the Poincaré map

To compute the Poincaré map of EEG data, as a first step, a notch filter is used to eliminate the 50 Hz frequency originated from the power line. Next, baseline drift (DC shift) was subtracted from each data set using a windowed moving average filter with window size of 101 samples. After that, to select correct peaks of the signal, amplitude, slope and width criteria were considered. Those peaks whose heights were smaller than a threshold value were eliminated. The threshold was adjusted manually by trial and error for each signal, however, in this paper it is defined as the average of the magnitude of the signal multiplied by a factor:

\[
P_{th} = \eta \times \frac{1}{N} \sum_{n=1}^{N} |s(n)|
\]

where \(P_{th}\) is the peak threshold, \(|.|\) is the absolute value, and \(\eta\) is the multiplier factor. This factor is set to 3.5, 3 and 2.5 for preictal, ictal and postictal periods, respectively. On the other hand, there are still some peaks which are above the threshold value but they should not be considered as correct peaks since the rising and/or falling edges are very small. The width criterion relates to the time interval between successive identified peaks. If this interval was less than a predetermined value (10 ms in this research), then the two peaks were averaged into one, so that false-positive peaks are avoided. In this way, fast transients due to electrical noise were eliminated. Moreover, visual inspection of the detected peaks was performed in several random segments of each part of the signal that led us to conclude that the selected thresholds are appropriate [28]. After detecting the peaks of the signal using the steps discussed above, IPIs were calculated and used as the time series for subsequent analysis. First-return scatter plots of the IPI values measured in seconds were constructed by plotting one IPI with respect to the next. An example for the preictal period of the patient number two is shown in Fig. 2.

As Fig. 2 shows, the scatter points are aligned across the horizontal and vertical axes and form an L shaped graph. This configuration has already been seen in [29]. Therefore, this can be modeled by an inverse quadratic function, i.e., \(y_{k+1} = d + 1/(a_1y_k^2 + b_1y_k + c_1)\) which has four unknown parameters \((a, b, c, d)\) that should be calculated. These parameters are linked to the frequencies of the peaks. However, a more specific interpretation of these parameters is difficult because no model was available that simulated the system [28]. To determine the Poincaré map parameters, the inverse quadratic function \(y = f(x) = 1/(ax^2 + bx + c) + d\) is approximated by a piece-wise linear function. A stochastic search algorithm such as Evolutionary Algorithm (EA) is exploited to minimize the cost function. The most important feature of EA is that there is no limitation (such as being convex or derivable) on the cost (fitness) function. Furthermore, it is not trapped by local minima, generally. The process of determining unknown parameters \((a, b, c, d)\) is fully discussed in Appendix A. Once these parameters are determined, analysis of the mapping function is performed according to the nonlinear dynamical system theory and will be explained in the next section.

Fig. 1. Illustration of the EEG signal for patient number two including ictal period.
3. Bifurcation analysis

Bifurcation is commonly used in the study of nonlinear dynamics to describe qualitative changes of the behavior of the system as one or more control parameters are changed. In this section, we analyze the dynamical behavior of the Poincaré map function using nonlinear dynamical system theory. Consider the first order dynamical system in the form of:

$$g(y_k) = y_{k+1} = d + \frac{1}{a_1 y_k^2 + b_1 y_k + c_1} \quad a_1, b_1, c_1, d \in \mathbb{R}$$

changing the variable $y - d = x$; we can write

$$x_{k+1} = \frac{1}{a_1 (x_k + d)^2 + b_1 (x_k + d) + c_1}$$

After some calculation, it is straightforward to show that this equation is equivalent to:

$$f(x_k) = x_{k+1} = \frac{1}{a x_k^2 + b x_k + c} \quad a, b, c \in \mathbb{R}$$

where

$$a = a_1$$
$$b = b_1 + 2a_1 d$$
$$c = c_1 + b_1 d + a_1 d^2$$

Consequently, we consider (5) as the basic equation to analyze. Throughout the paper, $\Delta = b^2 - 4ac < 0$ otherwise, there is at least one point at which the denominator of (5) is zero. To find the equilibrium points of (5), using Definition 1, at the fixed point $\bar{x}$ we have

$$x_{k+1} = x_k = \bar{x} \Rightarrow \frac{1}{a \bar{x}^2 + b \bar{x} + c} \Rightarrow a \bar{x}^2 + b \bar{x} + c = \frac{1}{\bar{x}}$$

A geometrical solution to (7) is illustrated in Fig. 3, assuming

$$a > 0, \quad b > 0$$

The intersections between the quadratic and the homographic functions demonstrate the position of the fixed points. This figure shows that there is only one positive fixed point. Indeed, satisfying conditions (8) leads the minimum point of the quadratic function ($x_{\min} = -b/2a$) to become a negative number. On the other hand, we can rewrite (7) as

$$a \bar{x}^3 + b \bar{x}^2 + c \bar{x} - 1 = 0$$
Fig. 3. A geometrical analysis to find the equilibrium point of the dynamical system (5). The blue curve is quadratic function and the red curve is the homographic function. (a) One positive fixed point; (b) one positive and one negative fixed points; (c) one positive and two negative fixed points. We refer to the positive fixed point as $\alpha$ in this paper. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

The cubic equation (9) has three real roots at most which are the equilibrium points of the dynamical system (5). The geometrical analysis in Fig. 3 explains that satisfying conditions (8) obligate cubic equation (9) to have one positive real root. Considering Fig. 2, we conclude that the positive equilibrium point is the only point we are interested in, since the other fixed points are not acceptable and thus irrelevant in our application. The positive fixed point is denoted as $\alpha$ throughout the paper.

To investigate the stability properties of the fixed point $\alpha$ and its bifurcation type that may occur, we used (5) and calculate the derivative of $f(x)$:

$$f'(x) = -\frac{2ax + b}{(ax^2 + bx + c)^2}$$

Using (10) and Definitions 3 and 4.b, we are able to find some explicit equations which describe where the flip bifurcation can occur:

$$f'(\bar{x}) = -1 \Rightarrow \frac{2a\bar{x} + b}{(a\bar{x}^2 + b\bar{x} + c)^2} = 1 \Rightarrow (a\bar{x}^2 + b\bar{x} + c)^2 = 2a\bar{x} + b$$
After some calculations and arranging the resulting equation with respect to $\bar{x}$, we have
\[
a^2\bar{x}^4 + 2ab\bar{x}^3 + (b^2 + 2ac)\bar{x}^2 + (2bc - 2a)\bar{x} + c^2 - b = 0 \tag{12}
\]
By substituting the only positive fixed point ($\bar{x} = \alpha$) into (12), the following equation is obtained
\[
a^2\alpha^4 + 2a\alpha^3 + (b^2 + 2ac)\alpha^2 + (2bc - 2a)\alpha + c^2 - b = 0 \tag{13}
\]
The recent equation demonstrates the locus of flip bifurcation points which is illustrated in Fig. 4. In this figure, not only conditions (8) are satisfied but also all the control parameters are varied based on the results that are obtained in the following section.

To find the conditions where the fold bifurcation could occur we used Definitions 3 and 4.a and started with (10) as follows:
\[
f'(\bar{x}) = 1 \Rightarrow \frac{2a\bar{x} + b}{(a\bar{x}^2 + b\bar{x} + c)^2} = -1 \Rightarrow (a\bar{x}^2 + b\bar{x} + c)^2 + 2a\bar{x} + b\bar{x} = 0 \tag{14}
\]
If we consider the conditions (8) for (14), there can be no positive fixed point, therefore all the terms in (14) would be positive numbers and their sum could not equal to zero. As a result, we applied the following conditions and investigated the fold or tangent bifurcation for this case:
\[
a > 0, \quad b < 0, \quad c > 0
\]
Satisfying conditions (15) leads to the geometrical analysis as shown in Fig. 5. Fig. 5(a) shows three real positive fixed points. If some of the parameter values are changed, the distance between equilibrium points is decreased. When the middle and right-side fixed points are coalesced, Fig. 5(b) is obtained. If we change the parameter values further, there is only one intersection between quadratic and homographic functions and consequently, there is only one fixed point. This situation is depicted in Fig. 5(c).

To explore the stability properties of the fixed points, we used Fig. 6 and Theorem 1. According to Theorem 1, when the slope of the inverse quadratic function at the fixed point is smaller than the slope of the identity function (equal to “1”), the fixed point is asymptotically stable (marked by filled circles). On the other hand, when the slope of the inverse quadratic function is greater than the slope of the identity function, the fixed point is unstable (marked by empty circle). It is noteworthy that it is possible to use (10) and calculate the derivative of f(x). However, the same results about the stability properties of the fixed points are obtained.

Changing the parameter values (a, b, c) leads to decrease in the distance between the right-side stable and (middle) unstable equilibrium points, so that at a critical value (bifurcation point) the equilibrium points coalesce and annihilate each other. This critical value separates two qualitatively different regimes. When parameters are near to but less than bifurcation point, the system has three equilibrium points and bistable dynamics. The quantitative features, such as the exact locations of the equilibria, depend on the particular values of the parameters, but the qualitative behavior remains unchanged no matter how close parameters are to the bifurcation value. In contrast, when parameters are near to but greater than the bifurcation value, the system has only one equilibrium point and monostable dynamic. In this case,
the system has only one attractor, and any solution starting from an arbitrary initial condition should approach to this attractor [8,12].

As Fig. 6 demonstrates, it is also possible to have another bifurcation between left-side and middle equilibrium points. In Fig. 7(a), we have plotted the graph of the inverse quadratic function $f(x)$ for a parameter value just above the critical value at which the bifurcation occurs. Fig. 7(b) illustrates this situation by plotting the cubic function (9). For parameters smaller than the critical value, two fixed points exist in this region: a stable and an unstable one (Fig. 7(c)). They both collapse for a critical value. When parameters are in the range of critical value, if an iteration $x_n$ approaches the tunnel between the bisector and the function $f(x)$, its value hardly alters through many iterations when passing the constriction, i.e. the sequence of $x_n$-values exhibit almost periodic, laminar behavior (Fig. 7(d)). If the tunnel has been passed, however, we observe uncontrolled leaps, until the trajectory is again captured by a tunnel zone. This corresponds to intermittent behavior.

The locus of the fold bifurcation points is illustrated in Fig. 8. In this figure, conditions of (15) are satisfied and moreover, all the control parameters are varied based on the results that are mentioned in the next section.

4. Results and discussion

In this section, it is shown that the suggested Poincaré map from the IPI plots is able to capture some features of the epileptic EEG data and provide insights into the underlying dynamics of the transition from preictal to ictal and then to postictal periods. Fig. 9 shows changes in the behavior of the first-return IPI plots before, during, and after the seizure for 100 s in patient number 2 with temporal lobe epilepsy [23]. The first-return IPI plot obtained for 40 s of preictal activity immediately before the seizure activity is shown in Fig. 9(a). As Fig. 9(a) shows, the sequences of IPIs are distributed along the horizontal and vertical axes, and consequently these points could be approximated by an inverted polynomial. This represents an estimate of the dynamics for the set of IPIs within the preictal period. The start of the seizure represents the synchronous firing of thousands of neurons in the vicinity of the recording electrodes. Fig. 9(c) is corresponding to the activity during the first 5 s of the seizure and displays a cluster of points that are located near the origin and the identity map. Fig. 9(d) illustrates the phase space for middle part of the seizure from 5 to 12 s during ictal activity and Fig. 9(e) shows the last part of the seizure from 12 to 20 s during ictal activity. Comparison of Fig. 9(c)–(e) reveals the progression of the IPIs on the diagonal line. These clusters of points which are arranged in different areas represent several frequencies that appear successively during the progression of the seizures. To illustrate the movement of the IPIs during the ictal period, the phase space for the patient numbers 15 and 16 are depicted in Fig. 10(a) and (b), respectively. Noteworthy that the postictal IPI plot is qualitatively similar to the preictal IPI plot and represents the L-shaped curve as shown in Fig. 9(b). As a consequence the continuous progression of the preictal–ictal–postictal activity could be captured by a one-dimensional Poincaré map that reveals possible bifurcation points and some dynamical regime observed in the recordings.
Fig. 7. (a) The plot of the inverse quadratic function (5) showing the tunnel zone (red bars). (b) The plot of cubic equation (9) after the bifurcation. (c) The plot of the cubic function (9) before bifurcation shows that the lateral points are asymptotically stable which are marked by filled circles and the middle point is unstable which is marked by an empty circle. (d) Sequence of points $x_n$ for a parameter value just above the critical value. When $x_n$ is passing the tunnel, its values exhibit almost periodic behavior. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 8. Locus of fold bifurcation points on $a \times b \times c$ space from different views. To clarify the pictures, several colors were used.
Fig. 9. IPI scatter plot during interictal, ictal and postictal activities in patient number two showing a seizure type of complex partial with the origin in the temporal lobe. Each IPI (in seconds) are plotted with respect to the next for (a) 40 s before the seizure, (b) 40 s after the ictal period, (c) the first 5 s of the ictal period, (d) the middle 7 s of the ictal period, (e) the last 8 s of the ictal period.
If we consider the Poincaré map instead of the continuous system, we can trace the bifurcation of the limit cycle to the bifurcation of the fixed points of the iterated map. In other words, in the Poincaré representation, periodic behavior appears as a fixed point located on the identity map (\(IPI_{n+1} = IPI_n\)). However, in Fig. 9 (c, d, e), due to the variability of the biological systems, a cluster of points near the identity map should be expected instead of ideally only one point on the diagonal line (bisectrix) in theoretical simulations to represent a periodic activity.

The parameter values of the Poincaré map function for the nine patients were calculated using the procedure mentioned in Section 2.3 and Appendix A. These values are listed in Tables 1 and 2 for preictal and postictal periods, respectively. The value in the parentheses is corresponding to the patient number in the original data set (EEG recorded in the Epilepsy Center of the University Hospital of Freiburg, Germany). Using the data shown in Tables 1 and 2, it is possible to trace the dynamical changes in the EEG recordings for seizure occurrence. Figs. 11 and 12 show how the parameter values of the Poincaré map function are changed for different patients. Each object represents a patient. For example, the square objects correspond to patient number 1. It is obvious that as we approach the seizure, the parameters move toward the bifurcation points. However, the exact path of the movement could not be traced. These shifts are demonstrated by the filled objects for each patient separately. After seizure incidence, the Poincaré map parameter values go far away from the bifurcation points. Similar to the preictal period, the exact path of the movement could not be identified. These shifting movements are illustrated by the empty objects for each patient. Similarly, in some patients, flip bifurcation occurs. Fig. 12 demonstrates how parameter values are changed as we move close to the seizure and then move away from it after the seizure occurrence. This provides a framework to understand the
Table 1
The parameter values of the inverse quadratic function for nine patients in preictal activity.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>80–40 s before seizure</th>
<th>40–0 s before seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$a_1$</td>
<td>$b_1$</td>
</tr>
<tr>
<td>1 (2)</td>
<td>254.85</td>
<td>−97.12</td>
</tr>
<tr>
<td>2 (4)</td>
<td>271.16</td>
<td>−69.91</td>
</tr>
<tr>
<td>3 (7)</td>
<td>1551.73</td>
<td>−67.97</td>
</tr>
<tr>
<td>4 (10)</td>
<td>830.05</td>
<td>−168.5</td>
</tr>
<tr>
<td>5 (12)</td>
<td>216.29</td>
<td>−126.5</td>
</tr>
<tr>
<td>6 (15)</td>
<td>464.11</td>
<td>−220.3</td>
</tr>
<tr>
<td>7 (16)</td>
<td>441.54</td>
<td>−108.6</td>
</tr>
<tr>
<td>8 (17)</td>
<td>773.43</td>
<td>−113.3</td>
</tr>
<tr>
<td>9 (21)</td>
<td>861.59</td>
<td>−554.3</td>
</tr>
</tbody>
</table>

Fig. 11. Locus of fold bifurcation points on (a) $a \times b \times c$ space, (b) $a \times b$ plane (c) $a \times c$ plane (d) $b \times c$ plane. Each object represents a patient. The filled objects illustrate the pathways approaching the ictal state while the empty objects show the pathways in postictal periods and returning from ictal event.
Table 2
The parameter values of the inverse quadratic function for nine patients in postictal activity.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>0–40 s after seizure</th>
<th>40–80 s after seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$a_1$</td>
<td>$b_1$</td>
</tr>
<tr>
<td>1 (2)</td>
<td>662.63</td>
<td>-520.19</td>
</tr>
<tr>
<td>2 (4)</td>
<td>517.3</td>
<td>-377.35</td>
</tr>
<tr>
<td>3 (7)</td>
<td>7744.9</td>
<td>-976.6</td>
</tr>
<tr>
<td>4 (10)</td>
<td>578.13</td>
<td>-103.89</td>
</tr>
<tr>
<td>5 (12)</td>
<td>512.10</td>
<td>-262.69</td>
</tr>
<tr>
<td>6 (15)</td>
<td>414.05</td>
<td>-210.82</td>
</tr>
<tr>
<td>7 (16)</td>
<td>553.54</td>
<td>-278.44</td>
</tr>
<tr>
<td>8 (17)</td>
<td>2079.4</td>
<td>-530.0</td>
</tr>
<tr>
<td>9 (21)</td>
<td>483.92</td>
<td>-241.33</td>
</tr>
</tbody>
</table>

Fig. 12. Locus of flip bifurcation points on (a) $a \times b \times c$ space, (b) $a \times b$ plane. Each object represents a patient. The filled objects illustrate the pathways approaching the ictal state while the empty objects show the pathways in postictal periods.

Fig. 13. (a) Bifurcation diagram for the Poincaré map function as a function of bifurcation parameter $b$ and $a = 250$, $c = 0.25$, (b) the corresponding Lyapunov exponent.
dynamics of approaching to seizure and then returning from it. Consequently, the main point is the presence of the bifurcation point that authenticates qualitative changes in the system’s behavior and is responsible for the transition to seizure.

Figs. 11 and 12 show that as the brain dynamics progress to the seizure, the system operates close to a bifurcation so that a weak stimulus can switch the dynamics. It has been proposed that bifurcations occur during epileptiform activity [35] and a possible source could be the imbalance between excitatory and inhibitory transmission of neurotransmitters. In fact, these cellular–molecular events put the system close to a bifurcation point [22].

To investigate the hidden and the rich variety of the dynamics within the described Poincaré function, the bifurcation diagram of (5) is created and is shown in Fig. 13(a). Considering $b$ as the bifurcation parameter, this graph indicates the steady state behavior of the system over a range of parameter values. From Fig. 13(a), we could find that there are several firing dynamic behaviors of IPIs, such as periodic, chaotic and quasi-periodic which appear alternatively with the variation of the bifurcation parameter $b$. These bifurcation diagrams represent a classical route to chaos through an inverse period-doubling cascade. Furthermore, we can notice several periodic windows, all of them are opened by a fold bifurcation and closed by a global bifurcation, namely being a crisis. Also, several other typical crises occur as the bifurcation parameter varies. Fig. 13(b) shows the corresponding Lyapunov exponent which is plotted as a function of $b$. A positive Lyapunov exponent characterizes the exponential divergence of the trajectories and, therefore, indicates the behavior as being chaotic.

Fig. 14. Lyapunov exponents of the inverse quadratic function (a) $a \times c$ plane and $b = -150$, (b) $a \times b$ plane and $c = 12$, (c) $b \times c$ plane and $a = 200$. 
5. Conclusion

Knowledge about the dynamics of epileptiform activity is an important scientific question with practical considerations in clinical control of seizure activity. Since the neural systems have strong nonlinear characteristics and are usually able to display different dynamics according to system parameters or external inputs, application of linear methods to signals generated by these nonlinear systems may result in spurious conclusions. In general, Fourier decomposition and similar methods are not adequate to disclose the nature of the bifurcations and chaotic dynamics [36]. As a consequence, the use of nonlinear analysis is justified and it provides additional insights into the intrinsic dynamics of the neuronal system.

The approach used in this paper was utilizing the Poincaré map function as a one-dimensional first-return map. The idea of using this approach is interesting as it characterizes a global viewpoint on the dynamics of neural tissue, which may complement more detailed models. We applied geometrical analysis which is commonly used in neuroscience [16,17] and chose the IPI as the variable to construct the mapping function. It was shown that amplitude time series can be converted to inter-spike interval time series without loss of information [31,32]. This validates the use of IPIs as a basic variable. By approximating the first-return plot to an algebraic equation, the Poincaré map function, a discrete representation of the original time series was provided. In this way, it is more convenient to obtain further quantitative insights into the dynamical regimes since these maps grasp the essential dynamical properties and simplify the mathematical study. An interesting practical application of such a procedure has been shown in the control of cardiac arrhythmia in humans using an adaptive nonlinear control method [10].

As proposed by other researchers [26], the dynamical characteristics were extracted from the geometry of the fixed points in the Poincaré map, specifically with regard to their stability and bifurcation characteristics. In this study, the invasive EEG recordings of 9 patients with temporal lobe epilepsy were utilized. Bifurcation analysis of the Poincaré map of these EEG recordings demonstrated that as the neuronal activity progresses from preictal state toward the ictal event, the parameter values of the Poincaré map move toward the bifurcation points. However, after seizure occurrence and in the postictal period, these parameter values move away from the bifurcation points. It was determined that the type III intermittency is the dynamical regime underlying some human seizures [29]. The emergence of intermittent behavior is always associated with the loss of stability of a periodic motion. In the type III intermittency, the periodic motion loses its stability because the eigenvalue of the characteristic matrix crosses the unit circle at $-1$ and the corresponding flip bifurcation becomes subcritical. Accordingly, we analyzed both flip and fold bifurcations, and it was showed that in some cases the flip bifurcation and in other cases the fold bifurcations are the dynamical regime underlying epileptiform events.

Regarding the obtained Poincaré map, it should be pointed out that bifurcation analysis is complicated using a 3-parameter form of the iterated map. Indeed, it is possible to simplify the iterated function (5) by rescaling the $x$...
variable to \( z = x^{3/\sqrt{a}} \). The resulting iterated map is given by 
\[ z(n + 1) = \frac{1}{z^2(n) + u \cdot z(n) + v} \]
where \( u = b/\sqrt{a^2} \) and \( v = c/\sqrt{a} \). The dynamics of this map are the same as those of the original system given by (5) and can be explored in a 2D parameter space rather than a 3D space. In this way, both data presentation and bifurcation analysis are simplified. This interesting point presents new opportunities for further investigation of the iterated map and relevant applications. This is addressed in near future. However, at the present time, the goal of this paper is to obtain and introduce the Poincaré map based on the scatter plots of IPI during preictal and postictal periods and then study the properties of the system. In other words, the paper focuses on the potential of the approach rather than an exhaustive treatment of a particular case which signify the preliminary nature of this work. Moreover, due to the high complexity of the brain, determining the basis of epileptic seizures in terms of a large number of interacting factors is a highly complicated task. Therefore, theoretical approaches that offer functional models and give insights for the seizures prediction/control mechanisms become more practicable. In this way, we provided that the obtained Poincaré map is able to capture some features of the epileptic EEG data and present insights into the underlying dynamics of the epileptic seizure. We believe that the offered Poincaré map constitutes a candidate for characterizing a global viewpoint on the dynamics of neural tissue which should be explored further in future studies. Finally, we conclude that more knowledge about the temporal distribution of seizures increases our insight into seizure dynamics and thus contributing to the development of appropriate prediction algorithms.

Acknowledgements

The authors would like to thank the anonymous and esteemed reviewers for their valuable comments on earlier versions of this paper. M. Amiri would like to thank Prof. Olivier David for his insightful suggestions and appreciates his assistance.

Appendix A. Parameter estimation method

For analyzing a nonlinear problem, a useful approach is to divide it into some linear parts and then solve the linear problems. The final solution is achieved by appropriate combination of the solutions. This procedure can lead to accurate results if the number of the linear parts is adequate. Here, the same concept is applied. Specifically, the inverse quadratic function \( y = f(x) = 1/(ax^2 + bx + c) + d \) is approximated by a piece-wise linear function with five control points which are demonstrated in Fig. A1. The control points are the maximum point of the curve, the two points located on the 0.1 maximum point of the curve and the two points located on the 0.01 height of the curve. A typical curve and its piece-wise linear approximation are shown in Fig. A1. By manipulating the configuration of the five control points, the resulted six piece-wise lines are adjusted to approximate the original curve as accurate as possible. Note that due to symmetry only three points of these control points are independent. However, we need all of them for measuring the distance of a scatter point from the curve (see next paragraph). Obviously, increasing the number of control points will change the approximation.

Next, the cost function for measuring the distance between the scatter points and the estimated curve should be defined. For each scatter point \( p_i = (p_{ix}, p_{iy}) \), \( i = 1, \ldots, N \), the Euclidian distance, \( d(p_i, L_j) \) is calculated between that point and each line \( L_j : \{ y = m_j \times (x - x_j) + y_j \} \). This is illustrated in Fig. A2. Therefore, the Euclidian distance can be computed using the following equation:

\[
 d^2(p_i, L_j) = \frac{(m_j(p_{iy} - y_j) + p_{ix} - x_j)^2}{1 + m_j^2} \tag{A1}
\]

Fig. A1. A graph of a typical inverse quadratic function and its piece-wise linear approximation with five control points. Due to symmetry, there are only three independent control points.
and the smallest value is considered as the distance between that point and the curve. Consequently, the total cost function is the sum of all distances of points, that is:

$$\phi(a, b, c, k) = \frac{1}{N} \sum_{i=1}^{N} d(p_i, L_{j_i})$$  \hspace{1cm} (A2)

where $j_i^* = \arg \min_{j=1,\ldots,5} d(p_i, L_j)$.

To determine the unknown parameters, a stochastic search algorithm such as Evolutionary Algorithm (EA) is exploited to minimize the cost function. The EA uses some mechanisms inspired by biological evolution such as mutation, cross-over and selection. The most important feature of EA is that there is no limitation (such as being convex or derivable) on the cost (fitness) function. Furthermore, it is not trapped in local minima, generally.

The EA algorithm starts with an initial population of solutions with size $N$, each of them is called an individual. At each iteration, the current generation is created using the mutation and cross-over mechanisms from the current population. After that, the $N$ individuals among the current generation are selected as the next generation. This process is repeated until the criteria of the problem are satisfied.

Technically, one of the important steps in executing an EA is how to define the representation of the problem’s parameters. In our problem, the unknown parameters that should be determined are $(a, b, c, d)$ which are the solutions of (A2). Although the EA mechanisms such as mutation and cross-over can be applied directly to find these unknown parameters, some modifications are needed to improve the search process of the EA. This is due to the fact that small changes in $a$, $b$, or $c$, may cause large changes in the shape of the estimated curve. Consequently, some morphological features such as height $(h)$, width $(w)$, $x$-component of the maximum point $(x_0)$ and the horizontal asymptotic $(d)$ are extracted from the inverse quadratic function. They are utilized in the optimization process instead of the original unknown parameters $(a, b, c, d)$. These new parameters are shown in Fig. A3.
The mathematical relations between the morphological and the original \((a, b, c, d)\) parameters are as follows:

\[
\begin{align*}
x_0 &= -\frac{b}{2a}, \\
h &= \left(\frac{-b^2}{4a} + c\right)^{-1}, \\
w &= \frac{1}{a}\sqrt{b^2 - 4a\left(c - \frac{1}{0.1h}\right)}, \\
a &= \frac{4}{w^2}\left(\frac{1}{0.1h} - \frac{1}{h}\right), \\
b &= -2 \cdot a \cdot x_0, \\
c &= \frac{1}{h} + \frac{b^2}{4d}, \\
d &= d \tag{A3}
\end{align*}
\]

The process of finding the unknown parameters using EA can be summarized by the following steps:

1. **Initialization stage.** A population with \(N\) individuals is created stochastically using Normal distributions for each parameters: \(N_j(\mu_0, \sigma_0^j), \quad j = x_0, h, w, d\)

2. **Mutation.** At iteration \(i\), each individual’s feature of the population is randomly selected with a uniform probability equal to \(P_M\) and its value is changed based on the corresponding Normal distribution \(N_j(\mu_0, \sigma_0^j), \quad j = x_0, h, w, d\). \(\sigma_i^j\) is calculated by the following equation

\[
\sigma_i^j = \sigma_0^j \times e^{\frac{-2i}{\text{max\_generation}}} + 0.01 \tag{A4}
\]

which \(\text{max\_generation}\) is the maximum number of iteration defined by the user. In this way, the variance of parameter changes decreases as the algorithm approaches to the final solution. At this stage, \(N\) new solutions (individuals) are created.

3. **Cross-over.** In this step, one tenth (0.1) pairs of the individuals are randomly selected and then the cross-over mechanism is applied to each pair which is shown in Fig. A4 schematically. Therefore, \(0.2 \times N\) new solutions are created.

4. **Fitness computing.** After generating new solutions, the cost function is calculated for each solution. To penalize those solutions that do not satisfy the condition defined in A2, a penalty term is added to the cost function and thus the final cost function could be written as

\[
\phi(x_0(v), h(v), w(v), d) = \sum_{i=1}^{N_p} d(p_i, L_j^i) + \gamma(b^2 - 4ac) \tag{A5}
\]

where \(\gamma\) is the weighting factor for the second term.

5. **Next generation selection.** After computing the fitness function (A5) for each individual, they are arranged based on their fitness value and the top \(N\) individuals are selected as the next population. The best solution is also stored at each iteration to monitor the evolution process.

6. **Ending criteria.** At the end of each iteration, two criteria are monitored to stop the algorithm. First, the number of iterations must not exceed from the user-defined maximum number of iteration. Secondly, if the best solution has a fitting error smaller than the user-defined error (\(\text{min\_error}\)), the running will stop.

The steps 2–6 are repeated until the algorithm terminates. The values of the EA parameters are listed in Table A1.
Table A1
The parameter values of the EA method.

<table>
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<tr>
<th>N</th>
<th>( a_{st}^0 )</th>
<th>( a_k^0 )</th>
<th>( a_w^0 )</th>
<th>( a_l^0 )</th>
<th>( x_0^0 )</th>
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References


