Chaos game representation of human pallidal spike trains

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Abstract Many studies have demonstrated the presence of scale invariance and long-range correlation in animal and human neuronal spike trains. The methodologies to extract the fractal or scale-invariant properties, however, do not address the issue as to the existence within the train of fine temporal structures embedded in the global fractal organisation. The present study addresses this question in human spike trains by the chaos game representation (CGR) approach, a graphical analysis with which specific temporal sequences reveal themselves as geometric structures in the graphical representation. The neuronal spike train data were obtained from patients whilst undergoing pallidotomy. Using this approach, we observed highly structured regions in the representation, indicating the presence of specific

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preferred sequences of interspike intervals within the train. Furthermore, we observed that for a given spike train, the higher the magnitude of its scaling exponent, the more pronounced the geometric patterns in the representation and, hence, higher probability of occurrence of specific subsequences. Given its ability to detect and specify in detail the preferred sequences of interspike intervals, we believe that CGR is a useful adjunct to the existing set of methodologies for spike train analysis.

Keywords Globus pallidus • Scaling exponent • Long-range correlation • Apomorphine • Chaos game representation

1 Introduction

Characterisation of the dynamics of neuronal spike trains has been an enduring challenge in which most of the efforts were based on classical statistical and information theoretic approaches [1, 2]. An earlier seminal paper by Mandelbrot and Gerstein [3] opened up the possibility of characterising the spike train or biological time series in general as a fractal or self-similar process, a possibility that has been demonstrated in many subsequent studies [4–6].

In a recent study, we observed that the interspike interval (ISI) time series from human internal pallidal (GPi) neurons exhibited scaling behaviour, thus characterising the fractal nature of a single GPi neuron as a nonlinear and nonequilibrium process in which the spike trains exhibit long-range correlation [7]. As most fractal analysis characterises the global patterns of average fluctuations as a function of resolution or size of the observation window [8], any fine temporal organisation would have been buried in the process. In the present study, we explore the possibility of a finer temporal organisation using an approach called chaos game representation (CGR). CGR was originally applied in various biological analyses such as ‘decoding’ patterns of long sequences of DNA [9, 10] and genomic signatures [11, 12] and characterising the relationship between different protein families [13]. The presence of geometric structures in CGR is an indication of the presence of a detailed temporal (or spatial) organisation, and conversely, a lack of any structure suggests that such an organisation does not exist.

2 Methods

2.1 Procedure and collection of data

The data were collected from 14 patients whilst undergoing pallidotomy, as previously described [7, 14, 15]. Informed consent was obtained from all patients. The procedure is reviewed annually by the Institutional Review Board of the Johns Hopkins University and NINDS-NIH. Anti-parkinsonian medications were discontinued 18 h prior to the surgery. The patients were put under domperidone, which is an anti-nauseating drug, 1 month before the surgery [16]. Apomorphine was started intraoperatively following preoperative analysis with doses ranging from 0.007 to 0.1 mg/kg determined by safety and tolerance levels. The data were obtained by inserting microelectrodes through a burr hole made by calculating the coordinates of GPi following the computer tomography scan. The striatum, GPi, and GPe (globus pallidus external) were identified by consistent patterns of neural activity, by passive movements of upper and lower extremities during the surgery both ipsilateral and contralateral to the recording site [14, 17, 18].

2.2 Postoperative analysis

The scaling exponent characterising the monofractal property for each pallidal spike train was first computed as described previously [7]. Briefly, given the functional equation denoting the self-similar relation $L(r) = kL(ar)$, where L is the fluctuations in ISIs measured at resolution r , a , a positive scale factor and k , a constant, a solution is the power-law relation $L(r) = Ar^\alpha$ where the scaling exponent α is the self-similarity parameter and A a constant. The scaling exponent α , which characterises the persistence of the underlying dynamics, was computed with the average wavelet coefficient method [19].

Whilst all sequences, random or otherwise, produce a pattern in the Sierpinski gasket or three-corner game, the four-corner game, or the Sierpinski carpet, produces pattern formation when there is a departure from randomness [20]. Pattern formation does occur in n -corner games with $n > 4$. However, when $n > 8$, patterns become hardly discernable [13, 20]—hence the choice of the four-corner game in the present study.

For a four-corner game, it would be natural to set the boundaries to create four equally spaced coarse-grained intervals. However, such an attempt would lead to two problems. Firstly, due to the scale-free, power-law, fat-tailed distribution of the ISIs, it is difficult, if not impossible, to estimate the total range within which to subdivide the four “equal” intervals. Secondly, as the power-law distribution is skewed towards the much more numerous shorter ISIs, with the longest interval hardly populated, defining the alphabet sequence by four equally spaced intervals would lead to a de facto three-corner game, which would fail to discriminate non-random from random sequences (see above).

To circumvent these problems, we first quantised the interspike intervals into four groups: From the histogram of interspike intervals, the cumulative frequency distribution was computed to determine the boundaries of four coarse-grained intervals, labelled a,

Fig. 1 An illustration of the construction of the CGR. In this example, given the sequence *bbca*, the following steps are taken: From centre to vertex *b*, mark midpoint 1 (arrowhead, address *b*); from 1 to *b*, mark midpoint 2 (address *bb*); from 2 to *c*, mark midpoint 3 (address *bbc*); from 3 to *a*, mark midpoint 4 (address *bbca*)

Fig. 2 A four-corner chaos game representation of the temporal organisation of ISIs of a human pallidal neuron (scaling exponent 0.77). Each of the four corners represents a coarse-grained interval, with *a* being the shortest and *d* the longest. The pattern was formed by an uneven distribution of points, each representing a specific ISI subsequence. For instance, the rectangles delineating sparsely populated regions provide evidence for the rare occurrence of the subsequence *aad*. Conversely, frequent occurrence of subsequences such as *bbdbb*, *bbca* and *bcab* is illustrated by the densely populated regions in the representation

b, *c* and *d*, such that each contained the same number of ISIs. When an ISI fell within the boundaries of a particular coarse-grained interval, the ISI was assigned the alphabet associated with that interval. Thus, the original ISI sequence was transformed into a sequence of alphabets necessary for the computation of the four-cornered CGR.

The CGR was constructed with the standard algorithm by Jeffrey [9] in which we labelled the upper right, lower right, lower left and upper left corners of the squares *a*, *b*, *c*, and *d*, respectively (Fig. 1). The procedure is illustrated in Fig. 1 [21]. Thus, accumulation of points in each address indicates a preference in the temporal sequence of interspike intervals. Consequently, any change in the fine temporal behaviours in the series could be observed as an alteration in the distribution of the density of points within the CGR [9, 20].

3 Results

The possibility of pattern formation in CGR of monofractal time series, and hence the presence and absence of specific subsequences, was investigated in pallidal neuronal spike trains with ISIs exceeding 12,000. This high ISI count or a long recording was found necessary for the detection of CGR patterns, and 9 out of 28 trains were observed to meet this criterion. The scaling exponents of these spike trains indicated persistent dynamics (0.76 ± 0.05). An example is the CGR pattern illustrated in Fig. 1 in which each point in the CGR (cf. Section 2 and Fig. 1) represents a specific subsequence of coarse-grained in-

Fig. 3 CGRs of three trains with different scaling values: **a** 0.66, **b** 0.73, **c** 0.81. Note a progression of ► prominence of patterns as the magnitude of the scaling exponent increases

Fig. 4 CGRs of three numerically generated trains with different known scaling values: **a** 0.6, **b** 0.8, **c** 1.0. As in Fig. 3, again note a progression of prominence of patterns as the magnitude of the scaling exponent increases

terspike intervals or alphabet. The occurrences of preferred and non-preferred subsequences manifest themselves, respectively, as densely populated and sparsely populated areas in the graph. For instance, the rectangles demarcating four sparsely populated regions on the left of Fig. 2 point to the relatively rare occurrence of the subsequence *aad*. Conversely, the three densely populated regions signify that the subsequences *dbdd*, *bbca* and *bcab* are prevalent in this pallidal spike train. Patterns with different preferred and non-preferred subsequences, and in varying degrees (see below), were observed in all nine spike trains investigated that met the criterion of high ISI count.

The second step was to examine the relationship between scaling exponent magnitude and the CGR pattern. When CGR analysis was applied, we observed that the temporal signatures of the spike trains (i.e. *preferred* interspike interval sequences) manifest themselves as a non-uniform distribution of the density of points (Fig. 2). Furthermore, this pattern became more pronounced in spike trains with higher scaling exponent values than those with lower ones (Fig. 3). This observation was verified when CGR analysis was applied to numerically generated data sets with known scaling exponents. As shown in Fig. 4, the CGR patterns became more distinct as the scaling exponent increased.

4 Discussion

We have observed that CGR is a useful approach for characterising the temporal behaviour of the interspike intervals. The emergence of patterns in CGR was correlated with the magnitude of the scaling exponent. There was an absence of patterns as the scaling exponent approached 0.5, whilst the pattern was significantly more pronounced when the scaling exponent values increased towards 1.0 in both experimental and numerically generated data (Figs. 3 and 4).

In the present study, the presence of preferred temporal sequences was graphically demonstrated by CGR on data obtained from single-cell recordings in the human pallidum. The presence of high or low density of points at particular locations in CGR is an indication of the existence of temporal signatures within the spike trains (cf. Figs. 2 and 3). These CGR patterns argue for the prevalence or an absence of specific subsequences which are sometimes difficult to detect by conventional statistical means [20]. For example, in Fig. 2, two high-density loci representing subsequences *bbca* and *bcab* indicate the prevalence of the temporal signature *bca* in the sequence of interspike intervals. Conversely, the sparsely inhabited regions on the left side of the representation indicate a relative absence of the subsequence *aad*. Thus, the emergence of CGR patterns in GPi trains argues for the contention that within the more global framework of fractal dynamics [7], there is a fine local temporal structure consistent with the globally persistent dynamics in human pallidal neurons. In CGR of spike trains with scaling exponents closer to 0.5, however, there is a more diffuse distribution of points (Fig. 3a), in accordance with the fact that these trains are more random in nature in which specific temporal orders are of chance occurrence.

The CGRs often exhibit self-similar patterns. As can be observed in Fig. 2, the infrequent subsequence *aad* spawns other sparsely populated, self-similar regions *aadd* and

aadd (Fig. 2) representing sequences containing the *aad* subsequence. Similarly, favoured subsequences would lead to self-similar, fractal patterns of high density of points.

It was not uncommon in the CGRs of some spike trains to show a paucity of points over a large region, e.g. in the region between *a* and *d* (Figs. 2 and 3c), indicating transitions of the kind from *a* to *d* and *d* to *a*, i.e. subsequences *ad* and *da*, were infrequent. On the other hand, the high-density aggregation of points on the rest of the plot representing transitions *ab*, *bc*, *cd* and *dc*, *cb*, *ba* attests to their high probability of occurrence. These observations are in accord with the persistent scaling characteristics of the spike trains in which a past increasing trend implies on average an increasing trend in the future and conversely for decreasing trends [8]. Further corroboration is provided by the CGR analysis of sequences with known scaling exponents (Fig. 4) in which the distinction between favoured and prohibited transitions becomes more pronounced as the dynamics becomes more persistent.

The recurrence plot [22] is another graphical technique for the analysis of favoured structural or temporal sequences. Whilst it has found wide application in physics and biology (see [23] for review), its application to the analysis of temporal organisation in neuronal spike trains has been scanty (see, e.g. [24]). In this approach, detection of favoured or recurring alphabet strings or subsequences requires the embedding of the ISI sequence in delay coordinates or similar strategies—a procedure not required in CGR analysis. The relative merit for sequence detection between CGR and recurrence plot analyses remains to be investigated. However, as shown in Figs. 3 and 4, CGR appears to excel in distinguishing the degree of persistence in these spike trains.

There are limitations to the present study. In order to establish CGR as a valuable tool, we need to have a formal assessment of the statistical significance of the patterns. The use of randomised surrogates [25, 26], as well as a larger sample size, may be promising avenues for exploration. Furthermore, as the neuronal activities were recorded from patients with Parkinson's disease, one should be cautious in generalising these observations to the normal CNS.

In conclusion, whilst the spike train, taken as a whole, exhibited monofractal scaling behaviour [7], we observed that within the global scaling statistic, there was a detailed temporal organisation characterised by the presence or absence of subsequences of interspike intervals or alphabets. In other words, whilst scaling analyses provide a broad statistical indicator of the presence of persistent or anti-persistent dynamics [8], CGR is complementary in furnishing a more detailed specification of the “alphabets” of persistence or anti-persistence. The question of whether these temporal signatures are merely a result of intrinsic neuronal properties, or indicators of network properties in action or both, will provide fertile grounds for further investigations in single-unit electroencephalogram and magnetoencephalogram studies, particularly in view of the fact that it is possible to associate changes in physiological conditions with changes in the fractal dynamics of a system [7, 27, 28].

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Authors' contributions MR was the primary author and, along with GR, wrote the programs and analysed the results. FAL, DSB, LV and HCK contributed to the writing of the paper. In addition, FAL performed the surgeries and acquired the data.

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