J. Neural Eng. **2** (2005) 11–16 doi:10.1088/1741-2560/2/2/002

Fractal spectral analysis of pre-epileptic seizures in terms of criticality

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Received 17 November 2004
Accepted for publication 17 January 2005
Published 8 March 2005
Online at stacks.iop.org/JNE/2/11

Abstract

The analysis of pre-epileptic seizure through EEG (electroencephalography) is an important issue for epilepsy diagnosis. Currently, there exist some methods derived from the dynamics to analyse the pre-epileptic EEG data. It is still necessary to create a novel method to better fit and explain the EEG data for making sense of the seizures' predictability. In this paper, a fractal wavelet-based spectral method is proposed and applied to analyse EEG recordings from rat experiments. Three types of patterns are found from the 12 experiments; moreover three typical cases corresponding to the three types of seizures are sorted out and analysed in detail by using the new method. The results indicate that this method can reveal the characteristic signs of an approaching seizure, which includes the emergence of long-range correlation, the decrease of anti-persistence behaviour with time and the decrease of the fractal dimension. The pre-seizure features and their implications are further discussed in the framework of the theory of criticality. We suggest that an epileptic seizure could be considered as a generalized kind of 'critical phenomenon', culminating in a large event that is analogous to a kind of 'critical point'. We also emphasize that epileptic event emergence is a non-repetitive process, so the critical interpretation meets a certain number of cases.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Epilepsy is a common neurological disease. There are 40–50 million people with epilepsy throughout the world, according to estimates of the World Health Organization [1]. EEG provides a window, perhaps the only practically accessible window at present, through which the dynamics of epilepsy can be investigated. Recently, it has been shown that EEG can further assist the goal of *predicting* epileptic seizures [1–4]. Efficient prediction of epileptic seizure would be useful for letting patients prepare for an imminent crisis (e.g. move to a safe location). Ultimately, if the epileptic patients could be notified of the forthcoming seizure on time, they would have a drug released to prevent the seizure from happening [5]. In brief, the prediction of epileptic seizure has the following benefits. One could be the development of novel diagnostic tools and treatments of epilepsy, for example, predication can enhance the likelihood of timely radioligand injection for SPECT scans, which can assist in identifying the epileptogenic focus. A second application may lead to the design of new, more effective drugs for the disruption of the seizures. A third application may develop and test new approaches to seizure control, such as drug release and electromagnetic stimulation. Finally, the prediction of epileptic seizure could indicate that further medication adjustments are necessary.

Recent studies show that a number of characterizing measures, derived from linear and nonlinear signal processing methods, are capable of extracting information from EEG to detect a pre-ictal phase [6], in particular, from the theory of dynamics. The properties of nonlinear dynamics (chaos)

[3] are firstly considered to serve as seizure precursors in human epilepsy. Chaos-based approaches assume the existence of a non-evolving low-dimensional attractor, and further require long, stationary, noiseless EEG data to compute the reconstructed attractor's properties. A detailed review of dynamics for prediction of epileptic seizures can be found in [1]. In fact, the actual epileptic EEG recordings are perhaps better described as transient signals embedded in noise, therefore the identification of chaotic dynamics is not adequate to explain the evolutionary characteristics of the pre-seizure phase. One possible alternative to the dynamical system methodology is to examine the scaling (fractal) properties in the EEG signals. Evidence of temporal self-similarity could explain both noisy characteristics and fractal structure.

In this paper, we employ a wavelet-based method (first proposed in [7]) to analyse the properties of the evolving fluctuations of the EEG signals in successive and short time segments. We demonstrate the capability of this analysis to conclusively identify the pre-seizure phase. Section 2 is a description of the relative clinical experiments and the method of analysis. The results are presented in section 3. Discussions are given in section 4.

2. Materials and methods

2.1. EEG recording

In this paper, 12 adult Sprague–Dawley rats (body weight of 321 ± 27 g) are used to study epileptic seizures in EEG recordings. During the experiments, every precaution is taken to minimize suffering to the animals. The rats are anaesthetized with an intraperitioneal (i.p.) injection of Nembutal (sodium pentobarbital, 65 mg kg^{-1} of body weight), and mounted in a stereotaxic apparatus. Two electrodes are placed in the epidural space to record the EEG signals from temporal lobe and frontal cortex, respectively (in this paper, however, we only analyse the EEG signals from the temporal lobe, the other channel has the same EEG characteristics due to the fact that all of the seizures are generalized). Then, the animals are housed separately postoperatively with free access to food and water, allowed 2 to 3 days to recover, and handled gently to familiarize them with the recording procedure. Each rat is initially anaesthetized with a dose of pentobarbital (60 mg kg^{-1}, i.p.), while constant body temperature is maintained (36.5–37.5 °C) with a piece of blanket. The degree of anaesthesia is assessed by continuously monitoring the EEG, and additional doses of anaesthetic are administered at the slightest change towards an awake pattern (i.e., an increase in the frequency and reduction in the amplitude of the EEG waves). Finally, bicuculline i.p. injection is used to induce in the rat generalized epileptic seizures. EEG signals are recorded using an amplifier with band-pass filter setting of 0.5–100 Hz. The sampling rate is 200 Hz, and the analogue-to-digital conversion is performed at 12-bit resolution. At the end of the experiments, the animals receive an overdose of pentobarbital. The recorded EEG data are used to identify a seizure onset reference time. A clear electrographic seizure discharge in EEG is first selected; then we look backwards in the record for the earliest EEG change from baseline that is associated with the seizure by a simple statistic method. The earliest EEG change is considered as the seizure onset reference time. Then, we look slowly forwards in the record observing the video recorded. Once we find that the rat shows specific or different movement or behaviour (not normal waking behaviour) including convulsion, sudden jerky movements, and so on, we select this time as the seizure onset beginning. Therefore, the duration of the pre-seizure possibly includes the increased early EEG activity, as shown in figures 1 and 2. The detailed recordings of 12 rats can be found in [16].

2.2. Wavelet spectrum

Fourier transform decomposes a signal into *infinite* length sine and cosine. This method effectively loses time localization information of a signal because sine and cosine functions do not decay. Differently, continuous wavelet transform (CWT) decomposes a signal into a series of compounds by small wavelet functions, so it offers very good time–frequency localization of the signal. So far, the CWT is a powerful tool to construct a time–frequency representation of a non-stationary signal. Also, it is found that the localized wavelet coefficients are well suited for analysing EEG data such as transient and evolutionary phenomena.

Wavelet coefficients $W_x(a,\tau)$ are produced through the convolution of a parent wavelet function $\psi(t)$with a signal $x(t)$,

$$W_x(a,\tau) = \frac{1}{\sqrt{|a|}}\int x(t)\psi\left(\frac{t-\tau}{a}\right)\mathrm{d}t, \qquad (1)$$

where a and τ denote the scale and local centre of the analysing wavelet. In this study, a Morlet wavelet is used, $\psi_0(t) = h(t)\,\mathrm{e}^{\mathrm{i}\omega_0 t} = \pi^{-1/4}\,\mathrm{e}^{\mathrm{i}\omega_0 t}\,\mathrm{e}^{-t^2/2}$, where $h(t)$ is a real-valued symmetric window function, ω_0 is the nondimensional frequency ($\omega_0 = 8$ in this paper). For a discrete EEG sequence x_n, CWT is defined as the convolution of x_n with a scaled and translated version of $\psi_0(t)$:

$$W_s(n) = \sum_{n=0}^{N-1} x_n\,\psi_0^*\left(\frac{(n-n)\,\mathrm{d}t}{s}\right) \qquad (2)$$

where $*$ indicates the complex conjugate. By varying the wavelet scale s and translating along the localized time index n, one can construct a picture that shows both the amplitude of any features versus the scale and how this amplitude varies with time. By replacing s by frequency f, the wavelet spectrum of the discrete sequence x_n can be defined as

$$S(f) = \bar{W}^2(f) = \frac{1}{N}\sum_{n=0}^{N-1}|W_f(n)|^2. \qquad (3)$$

An advantage of wavelet spectrum is that it can provide unbiased and consistent estimation of the true power spectrum of a time series [8, 9], and the wavelet families possess scale invariance (thus different kinds of scaling can be analysed by the same technique).

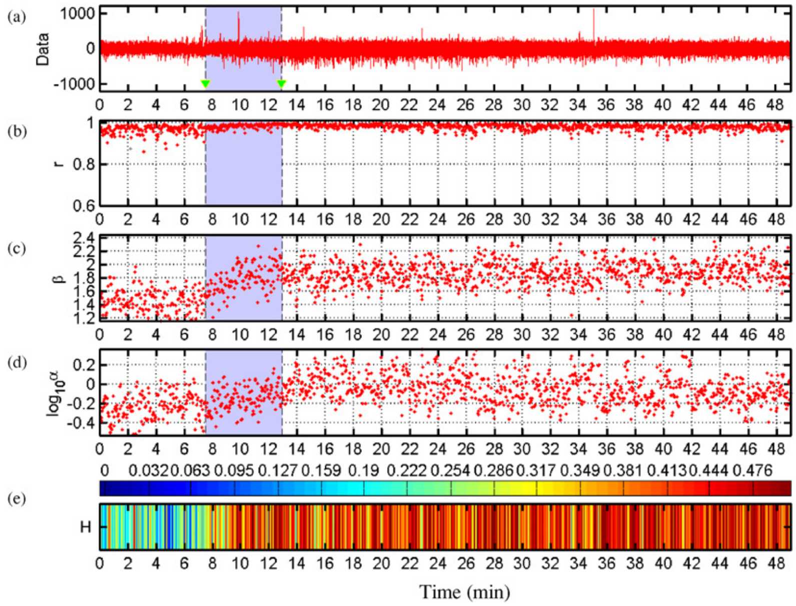

Figure 1. Fractal statistical analysis of a long-term EEG signal: (a) a long-term original EEG recording, (b) the linear correlation coefficient, r, of the power law with time, (c) the scaling parameter β of the power law $S(f) = \alpha f^{-\beta}$ with time, (d) the spectral amplification, α, with time and (e) the Hurst exponent, H, with time.

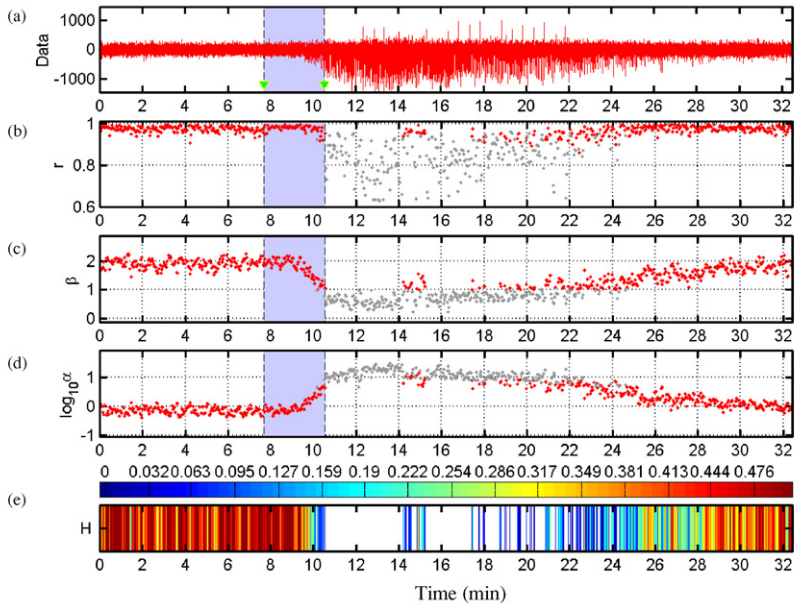

Figure 2. Fractal statistical analysis of a long-term EEG signal: (a) a long-term original EEG recording, (b) the linear correlation coefficient of the power law with time, (c) the scaling parameter with time, (d) the spectral amplification with time and (e) the Hurst exponent with time.

2.3. Power law and Hurst exponent

Any given time series may exhibit a variety of auto-correlation structures. For example, successive terms may show strong ('brown noise'), moderate ('pink noise') or no ('white noise') correlations with previous terms. One method for studying this effect is to assume a power law for the spectral density $S(f)$ of the time series, at least for a sufficiently wide range of frequencies f:

$$S(f) = \alpha f^{-\beta}. \tag{4}$$

The slope of the line fitting the log–log plot of the power spectrum by a least square method in the linear frequency range gives the estimate of the spectral exponent β. The associated linear correlation coefficient r is a measure of the overall quality of fit to the power law (4). The spectral amplification α quantifies the power of the spectral components following the power spectral density law (4). The characteristic values $\beta \sim 0$, $\beta \sim 1$ and $\beta \sim 2$ correspond to 'white', 'pink' and 'brown' noise, respectively.

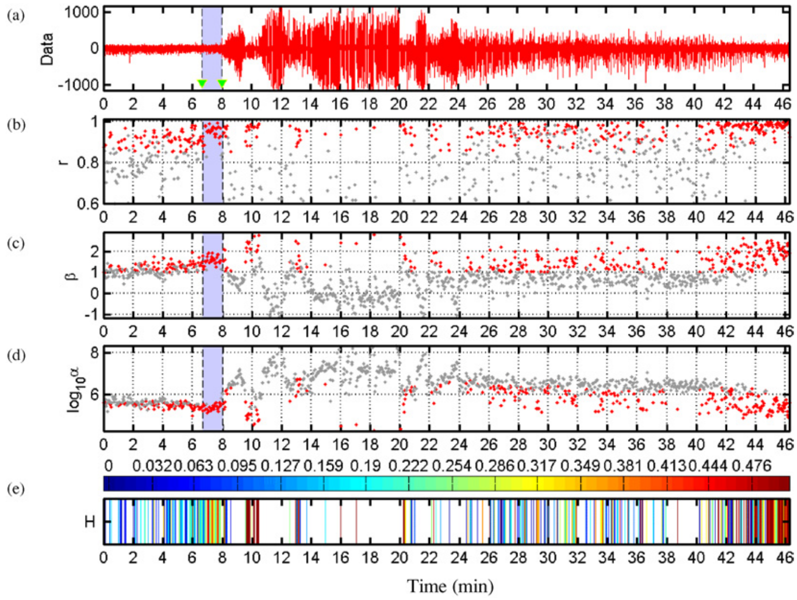

Figure 3. Fractal statistical analysis of a long-term EEG signal: (a) a long-term original EEG recording, (b) the linear correlation coefficient of the power law with time, (c) the scaling parameter with time, (d) the spectral amplification with time, (e) the Hurst exponent with time.

An alternative approach for studying the characteristics of irregular time series is the widely used fractal Brownian motion (fBM) model [8]: an fBM time series $A(t)$ can be viewed geometrically as a *self-affine* curve, each part of which is a reduced and scaled image of the whole. The increment function $(A(t+h) - A(t))h^{-H}$ (where $h > 0$) of fBMs has a probability distribution independent of t where H (Hurst exponent) is an index describing the self-affine characteristics of the curve, or can be interpreted as a measure of the *roughness* of the time series $A(t)$. In terms of spectral analysis, the power spectral density of $A(t)$ is also proven to follow equation (4) with $\beta = 2H + 1$ [10]. Thus, the Hurst exponent is

$$H = (\beta - 1)/2, \tag{5}$$

which lies in the range of $0 < H < 1$ and characterizes the persistence or anti-persistence of the time series $A(t)$ [10]:

(i) The range $0 < H < 0.5$ ($1 < \beta < 2$) suggests anti-persistence behaviour in the time series, i.e., if the system increases in one period, it is more likely to decrease in the period immediately following, and vice versa. In this interval there are long-range anti-correlations falling off as a power law.

(ii) $H = 0.5$ ($\beta = 2$) suggests no correlation between the process increments, meaning the system is characterized by random fluctuations. The corresponding time series does not possess temporal correlations.

(iii) The range $0.5 < H < 1$ ($2 < \beta < 3$) suggests persistence of the time series, i.e., if the amplitude of the time series fluctuations increases in one time interval, it is more likely to continue increasing in the period immediately following. In this interval, there are long-range positive correlations falling off as a power law.

In this paper, the calculation process is listed as follows:

(i) the continuous wavelet transform is used to calculate the spectrum of short-term EEG data by equation (3);

(ii) the parameters α and β in equation (4) are estimated by a least square method;

(iii) the Hurst exponent H can be given by equation (5).

The change of these parameters can be used to describe the brain dynamic characteristics for different states, in particular before the seizures.

3. Results

More precisely, our results could be classified into three representative and distinctive categories: type I (four cases), type II (five cases) and type III (three cases). This is due to the fact that the epilepsy model in this paper is simple, only generalized epileptic seizures are induced. Three characteristic case studies are shown in figures 1–3, which belong to type I, type II and type III, respectively. The injection times for the three cases are at 7:29, 7:41 and 6:40 (m:s) and the seizure times at 12:55, 10:30 and 8:00 (m:s), respectively. The pre-epileptic seizure phase must exist within the two time intervals.

3.1. The fractal spectral analysis of case I

The linear correlation coefficient, r, is a measure of the goodness of fit to the power law (4), as shown in figure 1(b). There is a gradual increase of the correlation coefficient with time during the pre-epileptic period, as compared with those in the quiescence interval. The finding supports the the power spectral density $S(f)$ in the successive segments of the EEG data following the power law $S(f) = \alpha f^{-\beta}$, and the fractal structure of the EEG data in the pre-epileptic seizure interval becomes stronger. Figure 1(c) reveals a systematic precursory increase (from the region of 1 up to the region of 2) of the scaling exponent β as the seizure approaches, the β values are maximal at the tail of the pre-seizure state.

The spectral amplification, α, quantifies the intensity of the spectral components of the EEG fluctuations following the power law (4). Figure 1(d) reveals a continuous, significant increase of intensity (up to about an order of magnitude) as the epileptic seizure approaches. The behaviour of the spectral amplifications may reflect higher synchronization of the brain activity as the seizure approaches. We grey-code the values of the Hurst exponent, as shown in figure 1(e). The small values are at the white end of the spectrum, and large values are at the black end of the spectrum. Figure 1(e) reveals that the Hurst exponents constitute a 'Joseph's coat-of-many-colours' display: the H value fluctuates widely.

3.2. *The fractal spectral analysis of case II*

The analysis depicted in figure 2 reveals that a decreased level of organization characterizes the pre-epileptic seizure in this case. Indeed, the observed systematic shift of β exponents to lower values during the pre-seizure state signals the decrease of the spatial correlations in the EEG data (see figure 2(c)). We pay attention to the fact that the initiation of the epileptic seizure seems to come with a significant shift of r values far from the value $r = 1$ (see figure 2(b)). This evidence reflects that the quality of fit to the power law (4) dramatically decreases with time, the inherent 'memory' of the system is destroyed, and namely, the EEG data no longer behave as a temporal fractal. Briefly, the initiation of the epileptic seizure is accompanied with damage of the fractal organization in the pathologically activated population of neurons. It is obvious that the case demonstrated in figure 2 is in full disagreement with that shown in figure 1.

3.3. *The fractal spectral analysis of case III*

As can be seen in figure 3, case III seems to be situated between the above-mentioned two cases. More precisely, during the pre-seizure stage we discriminate a shift of r values to higher values, as well as a shift of β exponent to higher values, see figures 3(b) and (c). This behaviour is in agreement with the case shown in figure 1. However, during the seizure the dynamics seems to drastically diverge. We distinguish that time windows where the time series fluctuates with low amplitude alternate with time intervals characterized by strong fluctuations. It is found that the temporal evolution of the parameters β and r uncovers that in the aforementioned two categories of time intervals, the associated r and β parameters obtain high and low values correspondingly. On the conceptual side, this behaviour may reflect a switch between high and low orders of fractal organization having low and high amplitudes of fluctuation correspondingly.

4. Discussions

A hallmark of physiological systems is their extraordinary complexity. Accumulated experimental and theoretical evidence shows the presence of long-range power-law (fractal) patterns in the biological signals. In this paper, we apply fractal spectral based on continuous wavelet transform to analyse the epileptic EEG data, in particular we concentrate on the pre-seizure phase. At least, the following results can be summarized through the examinations of 12 real rats: (i) the seizure emergence is a complex, non-repetitive process even for an individual subject; (ii) the EEG data follow the power law during the pre-ictal phase, the quantification of this process can assist in predicting the epileptic seizures; (iii) the epileptic seizure could be considered as a critical phenomenon.

4.1. *Complexity of seizure emergence*

As we mentioned, our approach is motivated by the need to generate a rigorous measure of the degree of complexity of the EEG signal. It is the first time that the time-dependent variation of the parameters $\{r, \beta, \alpha\}$ has been used in the quantification of brain pathophysiology. Comparing the fractal spectral analysis of three cases (see figures 1–3), it is found that the seizure emergences of three cases are very different. In particular, the parameters β in these three cases have a very different pattern. This fact is due to the change of the inherent 'memory' of the system, destroyed in conjunction with the parameter r. The value of parameter r relies on the fractal structure of the EEG data. Figures 1(b) and (c) support that the fractal structure of the EEG data becomes stronger as the seizure approaches; figures 2(b) and (c) and figures 3(b) and (c) support that the seizure also occurs when the fractal structure of the EEG data is destroyed. Thus, we may suggest that the change of fractal structure of the EEG data could result in the occurrence of the seizures. The fractal laws observed corroborate the existence of memory in the underlying process, the current value of the EEG signals at the pre-seizure phase covaries not only with its most recent value but also with its long-term history in a scale invariant, fractal manner [11]; the system refers to its history in order to define its future (non-Markovian behaviour).

Figures 1–3(d) show that there is a common characteristic for the parameter α in the three cases, namely the parameter increases as the seizure approaches. The behaviour of the spectral amplifications may reflect higher synchronization of the brain activity as the seizure approaches. This finding is in line with the accumulated evidence that highly synchronized EEG activity occurs during epileptic seizures [6, 12]. Moreover, this finding may suggest that the precursory activity cannot be ascribed to uncorrelated events from each individual source, but rather to cooperative emission of numerous activated neurons.

Figures 1–3(e) show that the H value fluctuates widely for the different states. This means that EEG data include many fractal dimensions, and the EEG data are temporal multi-fractal. This finding further enhances the complex characteristics of the brain activity.

4.2. *Prediction of seizure*

The analysis of the EEG data depicted in figure 1 (case I) suggests that the impending epileptic event may distinguish itself by a progressively increased level of organization, which is in agreement with the current theories on epileptogenesis. This organization further increases during the seizure. In contrast, a decreased level of organization during the pre-seizure can be found in figure 2 (case II). The seizure is followed by damage of the fractal structures. The third case shown in figure 3 is between the aforementioned two previous cases. More precisely, the pre-epileptic period is more-or-less similar to that of case I, while the seizure behaviour is different. The above evidence suggests that seizure emergence is a complex, non-repetitive process, which is in agreement with [13]. The underlying mechanism of the epileptic event is complex, and the physical laws that govern the preparation of the epileptic event are not totally known. The key issue is whether distinctive alterations in associated dynamical parameters emerge as the epileptic event approaches. Indeed, the visually apparent 'patchiness' and evolution of the EEG signals suggests that different parts of each signal may have different scaling properties. This motivated us to investigate the temporal *evolution* of the dynamical fractal parameters r, β, α of the power law (1) of the EEG signals divided into short and successive segments, each of 1024 samples ($\sim$5 s). The results above (see figures 1, 2 and 3) show that the fractal parameters can well track the change of EEG data, the properties of the pre-seizure phase can be revealed for its prediction, which could be of practical diagnostic and prognostic use.

4.3. Seizure and criticality

A few years ago, Bak *et al* introduced the concept of 'self-organized criticality' (SOC) [14]. Characteristically, Worrell *et al* [15] have shown that in the epileptic focus the probability density of pathological energy fluctuations and the time between large energy fluctuations show power-law scaling relations, i.e., that the system evolves without characteristic time and length scale. These features are fundamental signatures of an underlying critical dynamics. In this paper, we find the EEG data have a $1/f^{\beta}$ behaviour in the power spectral intensity, i.e. the appearance of long-range power-law correlations. Indeed, our analysis reveals that numerous distinguishing features emerged during the transition from normal states to epileptic seizures: (i) appearance of long-range power-law correlations, i.e., strong memory effects; (ii) gradual enhancement of lower frequency fluctuations, which indicates that the electric events interact and coalesce to form larger fractal structures; (iii) decrease of the fractal dimension of the time series; (iv) significant acceleration of the pre-epilepsy energy release as the seizure is approached. On the basis of these similarities, it might be argued that the epilepsy may be also viewed as 'a generalized kind of phase transition'.

Acknowledgments

We would like to thank Dr G Lian for supplying the EEG data and Profeser J G R Jefferys for his helpful remarks to this manuscript. In particular, we should thank the two referees for constructive comments to improve the paper. This paper is partly supported by the Wellcome Trust and Advantage West Midland (AWM), UK.

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