The Loss of Multifractality in Migraines

Miroslaw Latka
Institute of Physics, Wroclaw University of Technology, Wybrzeze Wyspianskiego 27, 50-370 Wroclaw, Poland

Marta Glaubic-Latka
Opole Regional Medical Center Al. Witosa 26, 45-401 Opole, Poland

Dariusz Latka
Department of Neurosurgery, Opole Regional Medical Center, Al. Witosa 26, 45-401 Opole, Poland

Bruce J. West
Mathematics Division, Army Research Office, P.O. Box 12211, Research Triangle, NC 27709-2211, USA

(Dated: April 2, 2002)

We study the middle cerebral artery blood flow velocity (MCAf v) in humans using transcranial Doppler ultrasonography (TCD). The time series of the axial flow velocity averaged over a cardiac beat interval is found to exhibit clear multifractal properties for healthy subjects. We observe a loss of multifractality for subjects with migraine.

PACS numbers: 87.10 +e, 87.15 Ya

Migraine headaches have been the bane of humanity for centuries, afflicting such notables as Ceasar, Pascal, Kant, Beethoven, Chopin, and Napoleon. However, its aetiology and pathomechanism have not to date been satisfactorily elucidated. Herein we demonstrate that the characteristics of the time series associated with cerebral blood flow (CBF) significantly differs between that of normal healthy individuals and migraineurs. Migraine is considered by many to be a functional neurological disorder in which CBF autoregulation failure may be responsible for the onset of symptoms. The results of our data analysis support this interpretation.

Physiological signals, such as CBF time series, are typically generated by complex self-regulatory systems that process inputs with broad range of accessible values. Even though this type of time series may fluctuate in an irregular and complex manner, they frequently exhibit self-affine or fractal properties which can be characterized by a single global parameter – the fractal dimension $D$ or equivalently the Hurst exponent $H$ ($D = 2 - H$). The salient property of mathematical random fractal process is the existence of long-range correlations for $H \neq 1/2$. The studies of the cardiac beat-to-beat variability have shown the existence of strong long-range correlations in healthy subjects and demonstrated the breakdown of correlations in disease [3] (see also [3] and references therein). A similar pattern was observed in fluctuations of the stride interval in human gait. The strength of correlations was significantly reduced both by aging and a neurodegenerative disease. This effect is frequently referred to as the loss of complexity [4, 5, 6].

While the properties of monofractals are determined by the global Hurst exponent there exists a more general class of heterogenous signals known as multifractals which are made up of many interwoven subsets with different local Hurst exponent $h$. The statistical properties of these subsets may be characterized by the distribution of fractal dimensions $D(h)$. Ivanov et al [8] established that the healthy human heartbeat interval exhibits multifractal properties and uncovered the loss of multifractality for the life-threatening condition known as congestive heart failure. Anticipating our result, herein we find the loss of multifractality in the time series of middle cerebral artery blood flow velocity is almost entirely lost in subjects with "severe" migraine even in headache-free intervals.

A healthy human brain is perfused by blood flowing laminarily through the cerebral vessels providing brain tissue with substrates, such as oxygen and glucose. It turns out that CBF is relatively stable with typical values between 45 and 65 ml/100g of brain tissue per second, despite variations in systemic pressure as large as 100 Torr. This phenomenon is known as cerebral autoregulation and has been thoroughly documented not only in humans but also in animals [3, 4]. Changes in cerebrovascular resistance (CVR) of small precapillary brain arteries is a major mechanism responsible for maintaining relatively constant cerebral blood flow. For example, CVR may increase due to mechanoreceptor constrictions of these arteries caused by the elevation of intracranial pressure (ICP) and/or biochemically mediated constrictions associated with the decrease of CO\textsubscript{2} arterial content. It is worth pointing out that changes in local cerebral activity may affect the regional cerebral flow (rCBF).
The increase in metabolism leads to the local drop of extracellular pH (which is associated with the elevated production of CO₂, lactic acid, and other metabolites) which in turn enhances the rCBF.

These complex cerebral flow autoregulation mechanisms are supposed to be influenced or even to be fundamentally altered in many pathological states [1]. However, despite the significant advances in brain diagnostic imaging techniques many functional aspects of CBF regulation are not fully understood. For example, migraine – prevalent, hemicranial (asymmetric) headache is among the least understood diseases. The leading neurovascular theory identifies serotonin, a strong vasculomotoric agent, as the main biochemical factor. In the last several years, CBF in migraine patients has been studied using diverse techniques such as Xenon-133 uptake measurements, cerebral tomography (CT), single photon emission tomography (SPECT) and positron emission tomography (PET). Although the pathophysiology of migraine headache has not been unequivocally explained, some experimental data reveal clear interhemispheric blood flow asymmetry in some parts of brain of migraineurs even during headache-free intervals [12, 13, 14].

Transcranial Doppler ultrasonography enables high-resolution measurement of MCA flow velocity. Even though this technique does not allow us to directly determine CBF values, it may help to elucidate the nature and role of vascular abnormalities associated with migraine. Some previous studies have discovered significant changes in cerebrovascular reactivity in migraine patients [15]. In this work we look for the signature of the migraine pathology in the dynamics of cerebral autoregulation. In particular, we investigate the fractal and multifractal properties of the human MCAf v time series.

The dynamical aspects of the cerebral autoregulation were recognized by Zhang et al. [1]. Kemeny et al. [17, 18] applied the attractor reconstruction technique along with the Grassberger-Procaccia algorithm and the concept of surrogate data to look for the manifestations of the nonlinear dynamics in continuous waveforms of TCD signals. Rossitti and Stephensen [19] used the relative dispersion of the MCAf velocity time series to reveal its fractal nature. West et al. [20] extended this line of research by taking into account the more general renormalization-group properties of fractal time series. Both studies [19, 20] showed that the beat-to-beat variability in the flow velocity has a long-time memory and is persistent with the average value of the Hurst exponent $H = 0.85 \pm 0.04$, a value consistent with that found earlier for interbeat interval time series of the human heart.

We measured MCAf using the Multidop T DWL Elektronische Systeme ultrasonograph. The 2-MHz Doppler probes were placed over the temporal windows and fixed at a constant angle and position. The measurements were taken continuously for approximately two hours in the subjects at supine rest. The study comprised eight migraineurs (who used to experience 1-3 migraines per month) and five healthy individuals. The migraine group underwent the standard diagnostic procedures e.g. computer tomography, EEG) to exclude illnesses not associated with cerebral autoregulation. An example of a typical measured MCAf time series is shown in Figure 1 for the first thousand of the recorded beats of the subject’s heart. The total time series has over eight thousand data points for a two hour data record.

Successive increments of mathematical fractal random processes are independent of the time step. They are correlated with the coefficient of correlation $\rho$ which is determined by the formula $\rho^{2H} = 2 + 2\rho$. Thus for $H \neq 1/2$ there exist long-range correlations, that is, $\rho \neq 0$. It turns out the Hurst exponent also determines the scaling properties of the fractal time series. If $y(t)$ is a fractal process with Hurst exponent $H$, then $y_c = y(ct)/c^H$ is another fractal process with the same statistics. This type of scaling is called renormalization. The variance of self-affine time series is proportional to $\Delta^{2H}$ where $\Delta$ is the time interval between measurements. A number of algorithms which are commonly used to calculate the Hurst exponent are based on this property.

Herein we employ the detrended fluctuation analysis (DFA) introduced into the study of biomedical time series by Peng et al. [21]. Let $\{v_i\}_{i=1}^{N}$ be the experimental time series of the middle cerebral artery blood flow velocity (MCAf) $v$. First, the time series is aggregated: $y(k) = \sum_{i=1}^{k}(v_i - \bar{v})$, $k = 1, .., N$, where $\bar{v}$ is the average velocity. Then, for segments of the aggregated time series of length $n$ the following quantity is calculated:

$$F(n) = \left( \frac{1}{N} \sum_{k=n_0}^{n+n_0} [y(k) - y_{n_0}(k)]^2 \right)^{1/2},$$

where $y_{n_0}$ is a least square line fit to the data segment which starts at $n_0$ and ends at $n + n_0$. The bar in the above equation denotes an average over all possible starting points $n_0$ of data segments of length $n$. Thus, for a given data box size $n$, $F(n)$ gives the characteristic size of fluctuations of the aggregated and detrended time series. If the aggregated time-series is fractal then $F(n) \sim n^H$, so one obtains the Hurst exponent from a linear least-square fit to $F(n)$ on double log graph paper. However, West has emphasized [20] the importance of possible periodic modulations of quantities such as $F(n)$. These modulations are intimately related to the renormalization-group properties of fractal time series and may be accounted for with the help of the following fit function:

$$F_X(n) = n^H \exp[\alpha + \lambda \cos(\gamma \ln n)],$$

Here again the Hurst exponent is determined by the slope of the fitting curve, but now the curve also has a harmonic
modulation in the logarithm of the length $n$ of the data segment.

Fig. 2 shows the typical DFA analysis for a healthy subject. The circles in this figure are the calculated values of $F(n)$ and the solid line is the best renormalization group fit, cf. Eqn. (2). The best-fit parameters are given in the inset.

The average Hurst exponent obtained from ten measurements of healthy subjects is equal to 0.85 and coincides with the value reported previously [19, 20]. Surprisingly enough, the DFA analysis of 14 measurements of migraineurs yielded the average value of $H$ equal to 0.83. While the observed difference is insignificant, we emphasize that most of the measurements were performed in headache-free intervals. Our further studies will address the question as to whether the Hurst exponent changes during the migraine episode.

We have already pointed out that in order to describe the scaling properties of multifractal signals it is necessary to use many local Hurst (or H"older) exponents. For the scaling properties of multifractal signals it is necessary to use many local Hurst (H"older) exponents. For example, the Hölder exponent $h(x_0)$ of a function $f$ at $x_0$ is defined as the largest exponent such that there exists a polynomial $P_n(x)$ of order $n$ that satisfies the following condition [23, 24, 25, 26]:

$$|f(x) - P_n(x - x_0)| = O(|x - x_0|^h)$$

(3)

for $x$ in a neighborhood of $x_0$. Thus the Hölder exponent measures the singularity of a function at a given point. For example, $h(x_0) = 1.5$ implies that the function $f$ is differentiable at $x_0$ but its derivative is not. The singularity lies in the second derivative of $f$. The singularity spectrum $D(h)$ of the signal may be defined as the function that for a fixed value of $h$ yields the Hausdorff dimension of the set of points $x$ where the exponent $h(x)$ is equal to $h$ [20].

In Fig. 3 we compare the averaged singularity spectrum of the healthy subjects with that of migraineurs. It is apparent that the multifractal properties of migraineurs are significantly reduced which is reflected by the vastly contracted interval for the distribution of fractal dimension $D(h)$.

It seems that the changes in the cerebral autoregulation associated with migraine can modify the multifractality of MCA blood flow much more strongly than monofractal properties characterized by the single global Hurst exponent. The loss of multifractality may persist in some subjects even in pain-free intervals. The more detailed analysis of the clinical data will be presented elsewhere.

---

[1] J. B. Bassingthwaighte, L. S. Liebovitch, and B. J. West, Fractal Physiology (Oxford University Press, Oxford, 1994).
[2] C. K. Peng, J. M. Hausdorff, S. Havlin, H. E. Stanley, and A. L. Goldberger, Phys. Rev. Lett. 70, 1343 (1993).
[3] A. L. Goldberger, Nonlinear Dynamics, Fractals, and Chaos Theory: Implications for Neuroautonomic Heart Rate Control in Health and Disease (World Health Organization, 1999).
[4] J. M. Hausdorff, C. K. Peng, Z. Ladin, J. Y. Wei, and A. L. Goldberger, J. Appl. Physiol. 78, 349 (1995).
[5] J. M. Hausdorff, S. L. Mitchell, R. Firtion, C. K. Peng, M. E. Cudkowicz, J. Y. Wei, and A. L. Goldberger, J. Appl. Phys. pp. 262–269 (1997).
[6] B. J. West and L. Griffin, Fractals 6, 101 (1998).
[7] J. Wallaczek, ed., Self-Organized Biological Dynamics and Nonlinear Control (2000).
[8] P. C. Ivanov, L. A. N. Amaral, A. L. Goldberger, S. Havlin, M. G. Rosenblum, Z. R. Struzik, and H. E. Stanley, Nature 399, 461 (1999).
[9] D. D. Heistad and H. A. Kontos, Cerebral Circulation (Am. Physiol. Soc., Bethesda, MD, 1983), vol. III, chap. 5, pp. 137–182.
[10] O. B. Paulson, S. Strandgaard, and L. Edvinsson, Cerebrovasc. Brain Metab. Res. 2, 161 (1990).
[11] J. Olesen, Rinsho Shikeigaku 30, 1317 (1990).
[12] P. A. Battistella, Headache 30, 646 (1990).
[13] M. Mirza, Acta Neurol Belg 98, 190 (1998).
[14] T. S. Olsen and N. Lassen, Headache 31, 49 (1999).
[15] J. G. Heckmann, Cephalalgia 18, 133 (1998).
[16] R. Zhang, J. H. Zuckerman, C. Giller, and B. D. Levine, Am. J. Physiol. 274, H233 (1999).
[17] R. W. M. Keunen, H. Pijlman, H. F. Visee, J. H. R. Vikiegen, D. L. T. Tavy, and C. J. Stam, Neurophys. Res. 16, 353 (1994).
[18] R. W. M. Keunen, H. H. R. Bliegen, C. J. Stam, and D. L. T. Tavy, Ultrasound Med. Biol. 22, 353 (1996).
[19] S. Rossitti and H. Stephensen, Acta Physiol. Scand. 151, 191 (1994).
[20] B. J. West, R. Zhang, A. W. Sanders, J. H. Zuckerman, and B. D. Levine, Phys. Rev. E 59, 3492 (1999).
[21] C. K. Peng, S. V. Buldyrev, S. Havlin, M. Simons, H. E. Stanley, and A. L. Goldberger, Phys. Rev. E 49, 1685 (1994).
[22] J. F. Muzy, E. Bacry, and A. Arneodo, Phys. Rev. Lett 67, 3515 (1991).
[23] S. Mallat, A Wavelet Tour of Signal Processing (Academic Press, San Diego, 1998).
[24] J. F. Muzy, E. Bacry, and A. Arneodo, Phys. Rev. E 47, 875 (1993).
[25] E. Bacry, J. F. Muzy, and A. Arneodo, J. Stat. Phys. 70, 635 (1993).
[26] Computations of singularity spectra were made using LastWave software available at http://www.cmap.polytechnique.fr/bacry/LastWave/index.html.
FIG. 1: MCAfv time series for a healthy subject.

FIG. 2: DFA analysis of the MCAfv time series shown in Fig.

FIG. 3: Comparison of the averaged singularity spectrum $D(h)$ of the healthy subjects (a) with that of the migraineurs (b). The spectra were computed using the WTMM. The analyzing wavelet was the second derivative of the Gaussian. The spectrum in Fig. (a) is the average of 10 measurements of five subjects. The spectrum in Fig. (b) is the average of 14 measurements of eight subjects.