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WHAT A PHYSICIST CAN LEARN FROM A SOMNOLOGIST?

INTRODUCTION

During the great Depression the American humorist Will Rogers with his characteristic sarcasm pointed out that: "The money was all appropriated for the top in hopes that it would trickle down to the needy." Nowadays "Trickle-down economics" in United States politics refers to the idea that tax breaks or other economic benefits provided to businesses and upper income levels will benefit the less fortunate members of society by improving the economy as a whole. In a scientific rather than an economic context one observes that many or even most physicists are proponents of trickle-down physics. They believe that the development of medicine and life sciences can be and often is determined by the adoption of methods and techniques developed in the physical sciences. Such an opinion is not entirely without merit. It is difficult to envision modern medicine without sophisticated imaging such as computer tomography, nuclear magnetic resonance or positron emission tomography and radiotherapy that extends the life of thousands of cancer patients every year.

Physicists either intentionally or not often find themselves at the frontiers of medicine. In 1928 a neuro-psychiatrist Hans Berger started the series of publications on bioelectrical activity of human brain. His groundbreaking work was accepted by the medical community six years later. It took Alfred Lee Loomis, an investment banker turned physicist, only three years to extend Berger's work and uncover the structure of human sleep in his private lab in Tuxedo Park, New York. This colorful individual was also instrumental in the development of radar thereby contributing to the Allied victory in World War II. However, such interdisciplinary research is a reciprocal interaction from which physicists also benefit. This paper is our testimony to that benefit.

FRACTAL GEOMETRY AND FRACTAL TIME SERIES

The term fractal was coined by the late Benoit Mandelbrot who championed its use in all manner of social and natural phenomena (Mandelbrot 1977). Since a picture is worth a thousand words in Fig. 1 we illustrate the generation of a geometric fractal - Koch's snowflake. It is built by starting with an equilateral triangle, removing the inner third of each side, building another equilateral triangle of 1/3 the size at the location

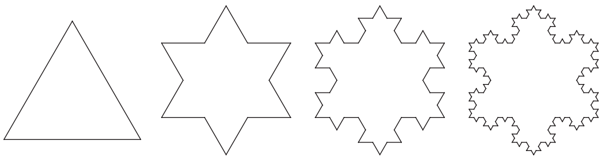

Fig. 1. The generation of Koch's snowflake fractal.

where the side was removed. This process is repeated indefinitely each time with the same contraction of scale size.

What geometric fractals have in common is the repeating pattern at every scale. If the replication is exactly the same at every scale (as in Fig. 1), it is called a self-similar pattern.

Let us look at the self-similar pattern from the different perspective by examining a different geometric fractal. In the left column of Fig. 2 we present a branching tree in which the outermost “tip” of the branch is magnified to reveal the same branching structure at the next smaller scale. It is worth pointing out that such branching may be found in the architecture of the human lung and vascular system (WEST 2013). A mathematical fractal has no characteristic scale size and its defining pattern proceeds to ever smaller and ever larger scales. On the other hand, a natural fractal always terminates at some smallest and largest scale and whether or not this is a useful concept for the process considered depends on the extent of the interval over which the process appears to be scale-free. A rule of thumb is that if the scale-free character persists over two orders of magnitude then the fractal concept may be useful.

However it is not just spatially that the fractal concept has proven to have utility, but also for the time interval between events. Let us focus on data in Fig. 3, that being the time series $W(t)$ of fractional Brownian motion (fractal time series for short) (FEDER 2013). Here it is not the geometric structure that is repeated at successive scales, it is the statistics of the fluctuations that are self-similar. The statistics of the time series are determined by the probability density $P(x,t)$ and the scaling is given by

$$P(x,t) = \frac{1}{t^H} F\left(\frac{x}{t^H}\right),$$

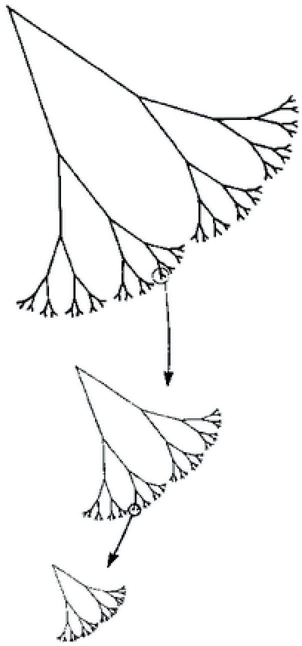

Fig. 2. Fractals are a family of shape containing infinite levels of detail.

The tip of each branch continues branching over many generations, on smaller and smaller scales, and each magnified smaller scale structure is similar to the larger form, a property called self-similarity. This is a treelike fractal described by fractal geometry.

where F is a normal distribution in the scaled variable x/t^H. In the time series data the scaling behavior of the fractal is seen through intermittent bursts of fluctuations interspersed between regions of relatively quiescent behavior. Upon magnification of a rectangular part of the top plot in Fig. 3, intermittent bursts between regions of relatively quiescent behavior can again be seen. More rigorously, the distribution function of the segment of the left trace with the horizontal axis magnified by a parameter b and the vertical axis by b^H according to the above equation is the same as that of the original trace. This scaling of the statistical distribution of the time series defines a fractal time series.

It turns out that the properties of the fractal time series defined above are determined by a single parameter – the Hurst exponent H ($0<H<1$). In particular, the standard deviation is proportional to t^H where t is the length of series. Said differently, the standard deviation increases as a power-law in time and the statistical distri-

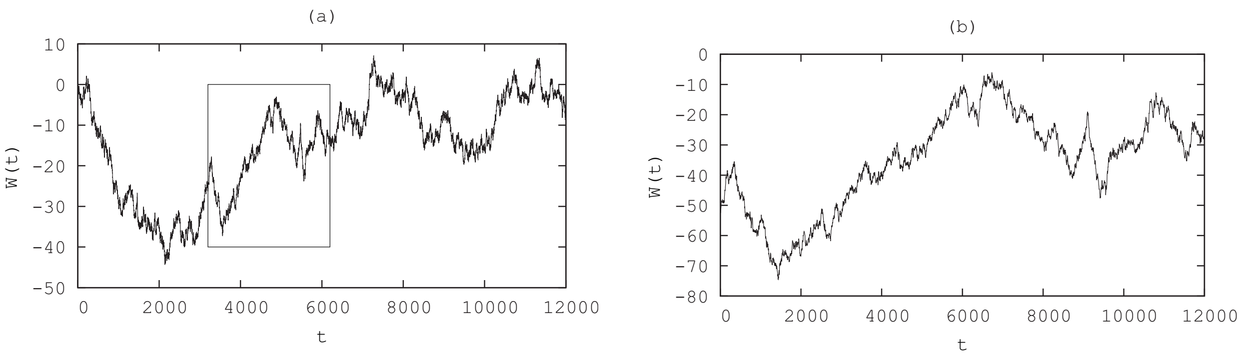

Fig. 3. Self-similarity (or more precisely self-affinity) of fractional Brownian motion.

The right plot is a blow-up of the rectangular region in the left plot. This region was rescaled by a factor of 4 along the x axis and by a factor of 2 along the y axis. The traces in both plots appear to "look the same". More precisely, the distribution function of the values for both traces are the same.

bution is normal. A number of algorithms that are commonly used to calculate the Hurst exponent are based on this scaling property.

SCALING IN PHYSIOLOGICAL TIME SERIES

Fractal fluctuations have been found in heartbeat dynamics (PENG *et al.* 1995), respiration (ALTEMEIER *et al.* 2000, MUTCH *et al.* 2005), human locomotion (HAUSDORFF *et al.* 1996), posture control (COLLINS and LUCA 1994) and cerebral hemodynamics (LATKA *et al.* 2004). See (WEST 2013) for a thorough review of scaling in physiologic time series. They have been the focus of interdisciplinary research for more than two decades. One outcome of this research has been a profound change in our understanding of the significance of homeostasis. Homeostasis – an organism's tendency to maintain, through negative feedback, approximately constant values of vital biological parameters, such as heart rate or blood pressure, has been the cornerstone of modern physiology since the turn of the twentieth century. However, the intrinsic variability of many physiological phenomena seems to reflect the adaptability of the underlying control systems and argues against the traditional view of homeostasis.

The view of many scientists is that the neurons of the human brain form the most complex dynamical network in existence. It is therefore hardly surprising that this complexity is reflected in electroencephalograms (EEG) – recordings of electrical activity of the brain from electrodes mounted on the scalp. Like most other biological time series, the EEG exhibits stochastic properties. Even when a person is quietly resting with eyes closed her EEG is irregular. However, an EEG time series is not simply uncorrelated noise but contains structure, such as alpha, beta, gamma and delta wave packets. Consequently, EEG waveforms are non-stationary and require special methods for their analysis. A number of research groups have argued that EEG time series have scaling properties, with a standard deviation that increases as a power law in time. The prevalent method used to determine the power-law index H and to take into account the issue of non-stationarity is detrended fluctuation analysis (DFA) (PENG *et al.* 1994). DFA is intended to remove the non-stationary components of the time series, called trends, and to provide a measure of the standard deviation of the detrended fluctuations as a function of the data window length. Let us elucidate this algorithm.

All physiological time series such as EEG are bounded. The largest amplitudes of EEG are observed during sleep. The amplitude of delta waves with frequencies between 0.5 and 2 Hz seldom exceeds 300 μV (SCHOMER and LOPES DA SILVA 2010) and the amplitudes of the other rhythms are significantly smaller. To transform the EEG signal into a potentially fractal time series we convert bounded measured values x_i into the unbounded process X_t

$$X_t = \sum_{i=0}^{t} (x_i - \bar{x}),$$

X_t is called a cumulative sum or profile. We may also say that we constructed a random walk X_t using the increments x_i for the step sizes. Imagine moving along the x axis and x_i being the length of the i-th step. Thus, X_t is the displacement from the starting point to your location after t steps. In the above formula $\bar{x}$ is the mean value of the experimental data. Then, X_t is divided into time windows of length L as illustrated in Fig. 4. For each window a local least squares straight-line fit is performed. This local trend is removed from the profile in each window and the standard deviation of the detrended data is calculated. We average the standard deviations over all windows of length L and plot the average value $F(L)$ as a function of L. A linear relationship on a double log graph, that is, *log F(L) versus log L*, indicates the presence of fractal scaling and the linear coefficient is the scaling *index H*.

It is worth emphasizing that DFA is one of the most frequently used algorithms for fractal analysis of experimental time series. The paper that introduced the DFA technique (PENG *et al.* 1994) has been cited over 2000 times as of 2013. The "DFA" query in PUBMED database returned about 500 papers focused exclusively on biomedical applications. The initial study of heart rate variability using DFA, that being to the intermittency of inter-beat interval time series, revealed the existence of two distinct regimes of scaling with the crossover taking place at approximately 10 heart beats (PENG *et al.* 1995). Interestingly enough, the short-time scaling exponent turned out to be clinically significant. For example, this meassure was the most accurate predictor of all-cause mortality in a cohort of 446 survivors of acute myocardial infarction (HUIKURI *et al.* 2000). The "two exponent" approach was used to quantify heart rate variability in various physiological conditions (MÄKIKALLIO *et al.* 1999, TULPPO *et al.* 2001, BECKERS *et al.* 2006, MOUROT *et al.* 2007), dynamics of arterial blood pressure (BECKERS *et al.* 2009, CASTIGLIONI *et al.* 2009) and cerebral blood flow (LATKA *et al.* 2004). Interestingly enough, until recently, no one proved in a mathematically rigorous way that DFA is applicable in short-time limit (IGNACCOLO *et al.* 2010b). To emphasize the importance of this problem in Fig. 5 we present the DFA analysis of EEG segment extracted from channel O2 of a polysomnographic recording (IGNACCOLO *et al.* 2010a). Some researchers suggested that there were not merely two but even three scaling regions in EEG signals as indicated in Fig. 5 by straight-line segments.

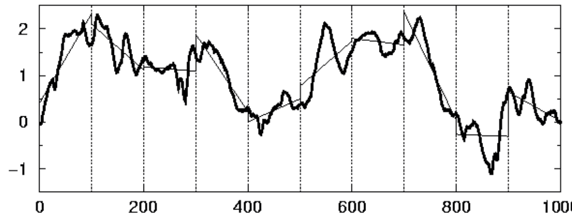

Fig. 4. The gist of DFA algorithm is to partition a cumulative sum of experimental data into non-overlapping windows and remove a polynomial trend in each of them.

The vertical dotted lines indicate windows of size L=100, and the solid straight line segments represent the linear trend estimated in each window by a linear least-squares fit.

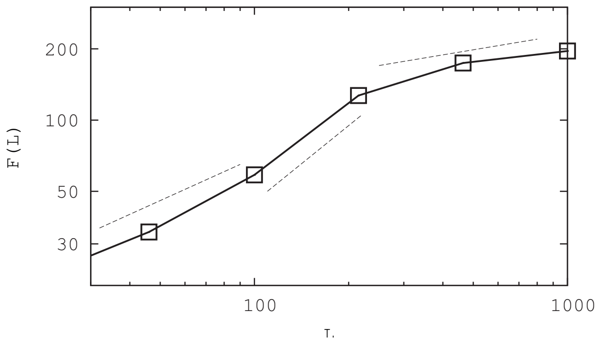

Fig. 5. DFA analysis of the EEG segment extracted from channel O2 of the polysomnogram (squares connected with solid line).

The dotted segments indicate three pseudo-scaling regions postulated by some researchers.

PARADOX OF THE ORNSTEIN-UHLENBECK LANGEVIN EQUATION

To address the question concerning the applicability of DFA to physiological data, we (IGNACCOLO *et al.* 2010b) adopted a simple stochastic model which exhibited short-time power-law scaling and incorporated a fundamental property of physiological control systems-negative feedback. This model, is known in physics literature as the Ornstein-Uhlenbeck (OU) Langevin equation (LINDENBERG and WEST 1990):

$$\frac{dX(t)}{dt} = -\lambda X(t) + \eta(t),$$

where λ is the dissipation rate and η is a random force with ordinary Gaussian distribution. We already know that in order to determine the scaling exponent it is necessary to calculate the standard deviation of a signal (with or without detrending) for data segments of different lengths. However, there are two ways of carrying out the average. In some experiments and in all computer simulations it is possible to generate number of data segments of a chosen length and average $X(t)$ and $X^2(t)$ over this collection of realizations of the time series to obtain a standard deviation. This way of doing the average is known as *ensemble averaging*. In medicine it is seldom possible. Imagine asking a patient to undergo repetitive EEG measurements to fulfill your need to average standard deviation over, let say 20 trials. It is obviously out of the question.

The second way to do an average is to partition the observational data into segments of increasing lengths, such as in the DFA algorithm described earlier, and to average the time series separately over each of the segments. This procedure is known as *time averaging*. But are these two approaches equivalent?

In general whether ensemble and time averages are equivalent is a subtle and difficult question to answer. When the two methods yield the same result the system is said to be ergodic, otherwise the system is non-ergodic. However, every student of physics knows that the OU Langevin model is stationary and ergodic and consequently "... One can then cut the record in pieces of length T (where T is long compared to all periods occurring in the process), and one may consider the different pieces as the different records of an ensemble of observations. In computing average values one has in general to distinguish between an ensemble average and a time average. However, for a stationary process these two ways of averaging will always give the same result...". This quote comes from the classic paper by (WANG and UHLENBECK 1945).

The reader should not be surprised that we were convinced that ensemble or time averaging should yield the same value for the standard deviation for the OU Langevin equation. We were wrong. In Fig. 6 we compare the dependence of standard deviation on the length of data segments for both type of averaging. It turns out that the long-time (asymptotic) value for time averaging is twice as large as that for ensemble averaging. When we realized the discrepancy it was not difficult to understand the reason and analytically calculate the values of the standard deviation for both ensemble and time averaging.

The question arises as to whether our unexpected discovery may be of interest to someone other than a statistical physicist. The standard deviation is certainly the most often used measure of time series variability. In light of the difference between ensemble and time averaging one can easily envision the situation when their simultaneous application appears rational but ultimately leads to a systematic error. For example, one may perform the measurements on a cohort of subjects to determine variability of a physiological quantity. However, when the variability for a given patient is compared with that of a cohort one may be inclined to improve the statistics by cutting the time series into pieces and performing averaging over them. We now know that this may lead to gross overestimation of the standard deviation, see the curves in Fig. 6.

We must admit as physicists that we feel that we benefited the most from this interdisciplinary research. We were able to identify the fundamental property of time series analysis using the model which has been the integral part of statistical physics since its inception. Unfortunately, we understood the pitfalls and limitations of application of fractal analysis to EEG signals (IGNACCOLO *et al.* 2010a). Nevertheless, when a somnologist

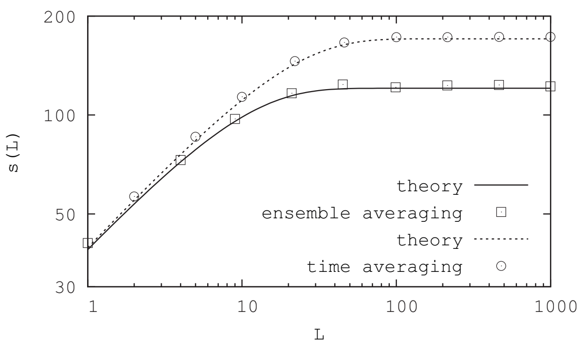

Fig. 6. Standard deviation for the computer simulation of the OU Langevin model for ensemble (squares) and time (circles) averaging.

Solid and dotted lines are the plots of the corresponding analytical formulas.

invites you to a research project do not reject the offer out of hand. You may not only help him/her to solve some research problems but you may learn, as we did, something totally unexpected.

WHAT A PHYSICIST CAN LEARN FROM A SOMNOLOGIST?

Summary

There is controversy concerning the proper fractal scaling of human EEG. In order to resolve it we applied the most commonly used algorithm — detrended fluctuation analysis (DFA) to the time series generated using a fundamental model of statistical physics: the Ornstein-Uhlenbeck Langevin equation whose scaling properties can be determined analytically. In the process we uncovered the totally unexpected difference between time and ensemble averaging for this stationary and ergodic model.

CZEGO FIZYCY MOGA NAUCZYĆ SIĘ OD BADACZY SNU?

Streszczenie

Długozasięgowe, fraktalne fluktuacje zaobserwowano w wielu fizjologicznych szeregach czasowych. Wyznaczenie fraktalnych współczynników skalowania sygnałów elektroencefalograficznych (EEG) napotkało na trudności związane ze słabym zrozumieniem własności jednego z najczęściej stosowanych algorytmów statystki fraktalnej — DFA (ang. detrended fluctuation analysis). W celu rozwiązania tego problemu przeprowadziliśmy analizę DFA szeregów czasowych wygenerowanych za pomocą równania Ornstein-Uhlenbeck Langevin — fundamentalnego modelu fizyki statystycznej, którego własności mogą być opisane analitycznie. W trakcie badań odkryliśmy zaskakującą własność tego modelu dotyczącą różnic w sposobie obliczania wartości średnich za pomocą uśrednienia po czasie i po zespole statystycznym. Zaobserwowane różnice są w sprzeczności z powszechnie przyjętą interpretacją własności modelu Ornstein-Uhlenbeck Langevin sformułowaną 70 lat temu.

REFERENCES

Altemeier W. A., McKinney S., Glenny R. W., 2000. *Fractal nature of regional ventilation distribution*. J. Appl. Physiol. 88, 1551–1557.

Beckers F., Verheyden B., Aubert A. E., 2006. *Aging and nonlinear heart rate control in a healthy population*. Am. J. Physiol. Heart Circulat. Physiol. 290, H2560–H2570.

Beckers F., Verheyden B., Ramaekers D., Swynghedauw B., Aubert A. E., 2009. *Effects of autonomic blockade on non-linear cardiovascular variability indices in rats*. Clin. Exp. Pharmacol. Physiol. 33, 431–439.

Castiglioni P., Parati G., Civijian A., Quintin L., Di Rienzo M., 2009. *Local scale exponents of blood pressure and heart rate variability by detrended fluctuation analysis: effects of posture, exercise, and aging.* IEEE Transact. Bio-Med. Engineer. 56, 675–684.

Collins J. J., Luca C. J. De., 1994. *Random walking during quiet standing*. Phys. Rev. Lett. 73, 764–767.

Feder J., 2013. *Fractals.* Springer, US.

Hausdorff J. M., Purdon P. L., Peng C. K., Ladin Z., Wei J. Y., Goldberger A. L., 1996. *Fractal dynamics of human gait: stability of long-range correlations in stride interval fluctuations*. J. Appl. Physiol. 80, 1448–1457.

Huikuri H. V., Makikallio T. H., Peng C.-K., Goldberger A. L., Hintze U., Moller M., 2000. *Fractal correlation properties of r-r interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction*. Circulation 101, 47–53.

Ignaccolo M., Latka M., Jernajczyk W., Grigolini P., West B. J., 2010a. *Dynamics of electroencephalogram entropy and pitfalls of scaling detection*. Physic. Rev. E 81, 1–9.

Ignaccolo M., Latka M., West B. J., 2010b. *Detrended fluctuation analysis of scaling crossover effects*. Europhysic. Lett. 90, 10009.

Lindenberg K., West B. J., 1990. *The nonequilibrium statistical mechanics of open and closed systems.* Wiley-VCH.

Latka M., Glaubic-Latka M., Latka D., West B. J., 2004. *Fractal rigidity in migraine*. Chaos, Solitons Fractals 20, 165–170.

Mäkikallio T. H., Koistinen J., Jordaens L., Tulppo M. P., Wood N., Golosarsky B., Huikuri H. V., 1999. *Heart rate dynamics before spontaneous onset of ventricular fibrillation in patients with healed myocardial infarcts*. Am. J. Cardiol. 83, 880–884.

Mandelbrot B. B., 1977. *Fractals: form, chance and dimension.* W. H. Freeman & Company.

Mourot L., Bouhaddi M., Gandelin E., Cappelle S., Nguyen N. U., Wolf, J.-P., Regnard J., 2007. *Conditions of autonomic reciprocal interplay versus autonomic co-activation: effects on non-linear heart rate dynamics.* Autonom. Neurosci. Basic Clinic. 137, 27–36.

Mutch W. A. C., Graham M. R., Girling L. G., Brewster J. F., 2005. *Fractal ventilation enhances respiratory sinus arrhythmia.* Respirat. Res. 6, 41.

Peng C. K., Havlin S., Stanley H. E., Goldberger A. L., 1995. *Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series*. Chaos 5, 82–87.

Peng C.-K., Buldyrev S. V, Havlin S., Simons M., Stanley H. E., Goldberger A. L., 1994. *Mosaic* *organization of DNA nucleotides*. Phys. Rev. E, 49, 1685–1689.

SCHOMER D. L., LOPES DA SILVA F., 2010. *Niedermeyer's electroencephalography: basic principles, clinical applications, and related fields*. LWW.

TULPPO M. P., HUGHSON R. L., MÄKIKALLIO T. H., AIRAKSINEN K. E., SEPPÄNEN T., HUIKURI H. V., 2001. *Effects of exercise and passive head-up tilt on fractal and complexity properties of heart rate dynamics*. Am. J. Physiol. Heart Circulat. Physiol. 280, H1081–H1087.

WANG M., UHLENBECK G., 1945. *On the theory of the Brownian motion II*. Rev. Mod. Phys. 17, 323.

WEST B. J., 2013. *Fractal physiology and chaos in medicine*. World Scientific.