Personalized Neurological Diagnostics from Biomedical Physicist's Point of View and Application of New Non-Linear Dynamics Methods in Biosignal Analysis

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***Abstract*—**We discuss importance of nonlinear methods of biosignal analysis for medical diagnosis and for assessment of applied therapy. We demonstrate several examples of applying Higuchi's fractal dimension method in Neurology and in other fields of Medicine. We discuss applications in sleep staging, vigilance monitoring, analysis of evoked EEG (photostimulation), epileptic seizures, neurofeedback, assessment of sensitivity to electromagnetic fields, of psychometric tests, of posturographic signals, as well as of seasonal affective disorder (SAD). Other examples concern Anesthesiology - monitoring the depth of anesthesia, Cardiology - analysis of Heart Rate Variability (HRV) and of stress level, Psychiatry - assessing effects of electroshocks. We also discuss the limitations of the concept of 'normal values' in Medicine. Nonlinear dynamics and deterministic chaos theory are proper physical frameworks for biomedical applications. Nonlinearity of dose-response behavior (hormesis) and informational interactions with electromagnetic fields illustrate limitations of 'normality' in Medicine and risk of using stiff standardized protocols. So, there is no alternative to Personalized Medicine provided by a well trained Medical Specialist.

***Keywords*—** biosignal, EEG, deterministic chaos, fractal dimension, HRV, nonstationarity, hormesis, nonlinear dynamics, norm, normative databases, personalized diagnostics.

I. Introduction

In Physics there exist well defined *normal values*. Normal values are not independent from one another - normal boiling temperature of water is $100^{\circ C}$ but only if the water is pure and under normal atmospheric pressure 760 mm Hg..

In Medicine normal values practically do not exist. The only such value seems to be 'normal body temperature' - 36.6°C. *It is an erroneous belief that in Medicine normal value equals population average value* – so called 'normative databases' e.g. of Quantitative EEG, no matter how large, do not give a possibility of 'reliable comparison' to decide if the given case is 'normal' or 'abnormal'.

Even the concept of a disease is *relative* and should take into account e.g. genetic differences between local populations. For example, sickle cell anemia is genetically inherited and in USA and Europe it is considered to be a serious blood disorder; but in Africa it gives evolutional advantage - those with sickle cell anemia are resistant to malaria.

A. Falsities

One can find papers stating that nonlinear methods require long stationary data and are very sensitive to noise while linear methods are robust to noise and perform well even for non-linear signals; and false statings like this: 'in case of EEG signals non-linear character is rather an exception' [1].

B. The Truth

The truth is exactly opposite – in biosignals like EEG linearity is rather an exception, only short epochs may be considered as linear.

Nonlinear methods may be applied also to linear signals, not oppositely.

There exist nonlinear methods (e.g. Higuchi's fractal dimension in time domain) that do not require long epochs, may be used in a window as short as 100 data points for analysis of any signal while being quite robust to noise.

Moreover, nonlinear methods can also be simple and intuitive, That is why I founded in 2007 an open access journal *Nonlinear Biomedical Physics* (BioMed Central, London) to facilitate interdisciplinary exchange of ideas concerning application of nonlinear dynamics in biomedicine between

Physicists and Mathematicians on one side, and Medical Doctors and Biologists on another side (cf.[2]). 'In reward' I have obtained letters like this:

"Dear Dr Klonowski,
I enjoyed reading your paper in the July issue of *Nonlinear Biomedical Physics*.
As a practising paediatrician with special interest in emotional

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and behavioural difficulties of young people, I thought your urging medical profession to adopt a new paradigm that integrates nonlinearity of our existance, couldn't have been more appropriate and timely. Thank you for helping non mathematicians like me to begin to understand this important field.

Dr Rashmin Tamhne, MD, FRCP
Consultant Paediatrician and
Hon Senior Lecturer in Child Development and Behaviour,
University of Leicester, UK."

C. 'Human Linearity Virus'

Many biomedical researchers is '*infected with Human Linearity Virus', HLV.* They 'think linearly', disregarding the facts that human brain is a complex nonlinear system, that complex nonlinear systems generate nonstationary nonlinear signals, and that appropriate analysis of such signals does need new nonlinear methods; otherwise while living in XXI century we will still be plunged in XIX century 'linear science' of Fourier and Markov.

II. Higuchi's Fractal Dimension

There exists many different methods of biosignal analysis. Even some scientists are not aware of shortcomings of such linear methods like e.g. Fast Fourier Transform (FFT). The most serious shortcoming of practically all linear methods is the fact that they are fully applicable only to stationary signals while biosignals are very, very nonstationary. However, medical community accepted and widely uses linear methods like FFT. On the other hand, there are more and more commercial software in use that is supposed to facilitate medical diagnosis, but the users, Medical Doctors, in most cases cannot really answer the question 'Do you understand what your computer *really* calculates?' because numerical calculations involved maybe based on a complicated mathematical model that additionally may be based on assumptions not known to the user; so the Doctor is rather not aware that the assumptions the calculations are based on may be not fulfilled by the analyzed signal, and so the results obtained on the screen may be very misleading.

In our Lab we have developed several nonlinear methods – fractal analysis, symbolic analysis, Empirical Mode Decomposition – for biosignal as well as bioimage analysis applied to medical diagnosis and assessment of influence of applied medical treatment (drugs, surgery). Here I will concentrate on Higuchi's fractal dimension method because of its simplicity and clarity and because the algorithm that calculates Higuchi's fractal dimension is very fast that makes it applicable for real-time calculations.

Higuchi's fractal dimension, D_f, is calculated directly from the analyzed signal. *Signal* denotes changes with time of the amplitude of some measured quantity. For example in the case of EEG this is changing with time of the electrical potential difference between an electrode placed on patient's scalp and another electrode that serves as the reference ('zero').

Everybody knows that a curve has Euclidean dimension equal 1 while a plane has dimension equal 2. Imagine an old EEG-apparatus that records EEG-signal with a pen as a curve on a moving paper tape. D_f , in fact, characterizes the curve that represents analyzed signal on a plane. If the device registers pure noise the tape surface (plane) will be filled out (smeared) completely, i.e. D_f in this case is close to 2.0 - the Euclidean dimension of plane; if the device registers simple signal e.g. one changing like a sine, the tape surface remains practically 'empty' (white), i.e. D_f in this case is practically equal 1.0 - the Euclidean dimension of a curve.

The trace drawn when registering *any* EEG-signal partially fills out the tape's surface and so it may be characterized by a D_f value between two extremes - 1.0. for a signal generated by a fully deterministic process and 2.0 for a signal generated by a fully stochastic process. There is absolutely no need 'to check if the signal is really chaotic' (cf. [3]). In fact, nothing really changes in the above arguments when a signal is observed on computer screen and registered numerically on a hard disk or memory stick instead of being drawn with a pen on a paper tape. Higuchi proposed a simple algorithm to calculate D_f of a signal registered in a numerical form ([4], cf. [2]). But .'fractal dimension' has several very different meanings. For example, Higuchi's fractal dimension should not be confused with fractal dimension of *attractor in the phase space,* such as so called *correlation dimension.*

Higuchi's fractal dimension may be calculated in a moving time window containing so few as ca. 100 data points. This way one obtains *running fractal dimension,* $D_f(t)$, that characterizes changes of *signal complexity*. Higher values of $D_f(t)$ correspond to presence of higher frequencies in the signal's Fourier spectrum (cf. [2]). Abrupt changes of $D_f(t)$ correspond to *signal's nonstationarities.* Because $D_f(t)$ compresses long epochs of raw data into much smaller D_f-epochs, such that the eyes can see the whole picture at once instead of viewing the original record 'page after page', it may make easier for Medical Doctors to choose which fragments of record are important and should eventually be further checked using other methods.

While running fractal dimension may be used to characterize short-lasting phenomena like eye blinking, when averaged over a longer period of time (mean fractal dimension) it also serves as a meaningful characteristic of analyzed biosignals.

III. Examples of Using D_F in Neurology

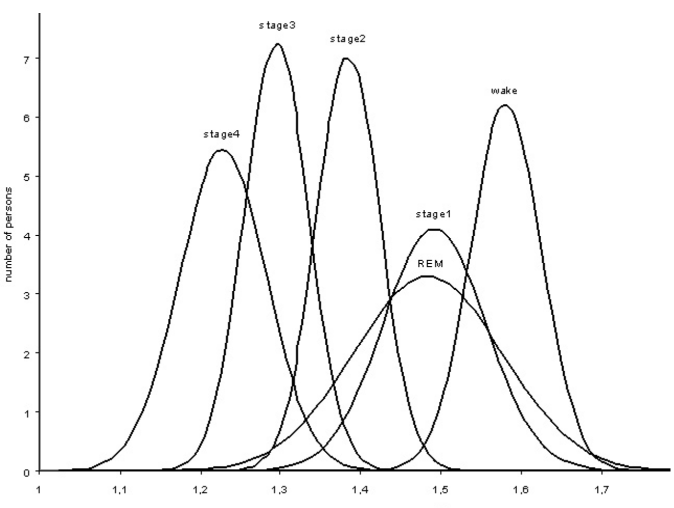
A. Automatic Sleep Staging

By comparing $D_f(t)$ of EEG-signals from polysomnograms of 15 healthy persons that had been analyzed 'manually' by the Medical Doctor specialized in sleep disorders we found that each sleep stage may be characterized by a certain range of $D_f(t)$:

wake:	$1.6 \leq D_f$
stage 1:	$1.525 \leq D_f < 1.6$
stage 2:	$1.385 \leq D_f < 1.475$
REM:	$1.475 \leq D_f < 1.525$
stage 3:	$1.305 \leq D_f < 1.385$
stage 4:	$D_f < 1.305$

Using such : $D_f(t)$: intervals we have programmed our automatic sleep stager. The hypnograms constructed by this stager applied to the same 15 polysomnograms have shown 49% concordance with the medical hypnograms when subdivision into 5 sleep stages were considered and 69% concordance with medical hypnograms constructed with subdivision into 3 stages (because of similar values of fractal dimension stage 1 and REM were statistically 'lumped together', and so were stages 3 and 4). Moreover, in this last case there were practically no differences in the ranges of $D_f(t)$ if we analyzed raw sleep-EEGs or sleep-EEGs from which artifacts had been removed by clinicians.

One should not forget that a medical hypnogram, done by a specially trained clinician, is based not just on EEG-signal but on the whole original polysomnogram that contains multi-channel EEG, ECG, EOG, and others biosignals; even despite of that, the accuracy of medical hypnograms is believed to be of order of about 70%..In fact, 'inter-operator differences', i.e. differences between clinicians specialized in sleep disorders when assessing the same polysomnogram may be even much, much greater [5]. By calculating $D_f(t)$:of several sleep-EEG analyzed by a clinician we could *individualize* our stager for the clinician by introducing into the stager $D_f(t)$: intervals that are appropriate for this sleep specialist.



. **Fig. 1**. Distribution of fractal dimension of EEG-signal (Current Source Density, CSD, on electrode C3) in various sleep stages in a group of 15 healthy persons.

B. Vigilance Monitoring

Like in practically all cases of quantitative characteristics used in medical diagnostics in general, and in neurological diagnostics in particular, one may not set 'normal values' of D_f even for 'absolutely healthy' person neither while awake nor in any stage of physiological sleep so big are interpersonal differences. Each individual is his/her own reference – only relative differences of D_f values make sense. Indeed, despite of interpersonal differences we observe the same *trend* in changes of fractal dimension of EEG-signal during physiological all-night sleep - D_f value is maximal while a person is awake and it decreases when sleep becomes deeper; for REM stage it again increases, but remains lower than while the person is awaken (Fig. 2).. Such trend we found in all sleep-EEG-signals that we have analyzed in our Lab.

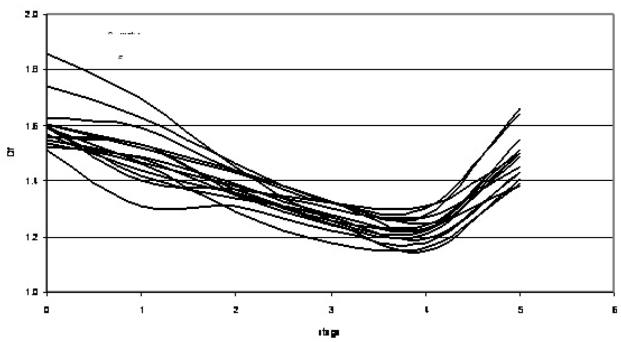


Fig. 2. Fractal dimension of EEG-signal in different sleep stages for 15 healthy persons. 0 - while awake; 1,2,3,4 - in sleep stages 1,2,3,4 respectively; 5 - in REM sleep. For convenience the values for each individual persons are connected by a line, but only the values for the numbers marked 0,1,2,3,4,5 on the horizontal axis are meaningful, calculated from CSD on electrode C3..

So, with similar computer program as that used for our automatic sleep stager it is possible to grasp when a person is falling asleep. i.e. when D_f of EEG-signal falls down from the value characterizing this person's EEG while awake. Such a device – small computer registering EEG and calculating in real time its D_f - could be used for vigilance monitoring e.g. of car drivers [6]. By measuring his/her EEG-signal's D_f while awake before starting the car engine the driver may *individualize* the vigilance monitor for his/her personal use to get alarmed when falling asleep while over the wheel.

C. Evoked EEG - Photostimulation

D_f of EEG-signal evoked by external stimulus clearly demonstrates the influence of the applied stimulus. For example, changes of D_f due to photostimulation that is routinely used in EEG-registration procedures show that brain reaction is the most intensive when a healthy peron is stimulated with light flashing with frequency of 18 Hz (Fig. 3). In some neurological diseases sensitivity to light may be changed.

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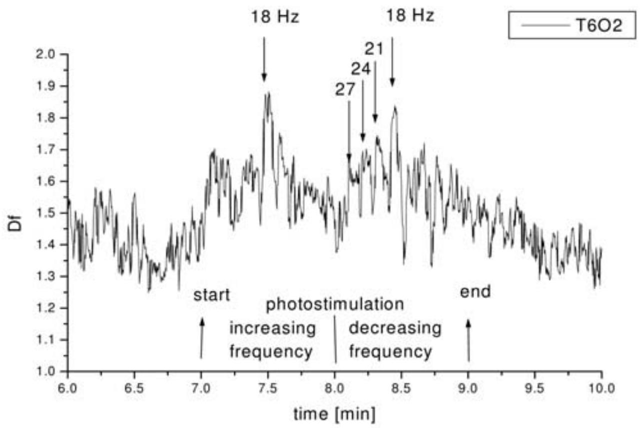


Fig. 3. Fractal dimension of EEG-signal T6-O2 of a healthy person evoked by photostimulation [2].

D. *Influence of Electromagnetic Fields*

Influence of external electromagnetic fields (EMF) on human brain is not fully understood, because it depends on so many individual characteristics of the brain at the given moment as well as on several characteristics of applied field and its changes in time. By comparing fractal dimension of EEG-signal registered under influence of the EMF (e.g. when the patient is lying down on a so called 'magnetic mattress') when the intensity of the applied field is different, we may find with high probability who is sensitive to the EMF and who is much less sensitive.

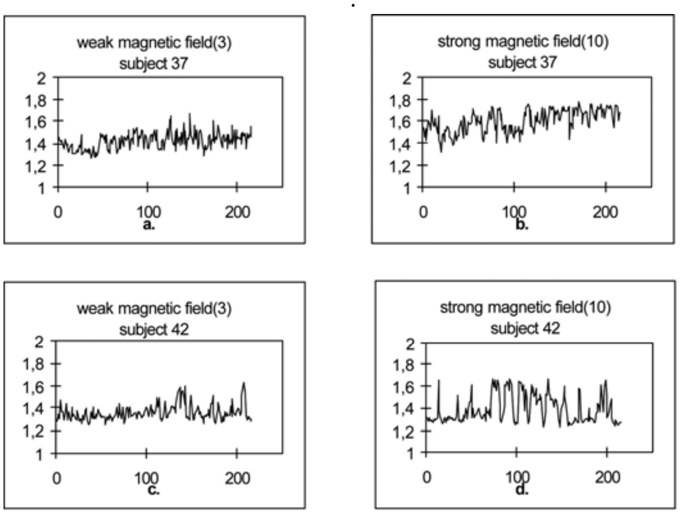


Fig. 4. D_f calculated for two healthy persons lying down on a 'magnetic mattress'. One unit on horizontal axes denotes 5 s. For the first 7 min. (84 units) magnetostimulation is "off"; for next 7 min. (75 to 168 units) magnetostimulation is "on"; then magnetostimulation is "off" again. In "weak" magnetic field (**a, c**) none of the subjects shows noticeable reaction; in "strong" magnetic field reaction of subject 42 is much more profound (**d**) than that of subject 37 (**b**).

So called '*norms of exposure*' to EMF mislead even Medical Doctors. They are based only on *thermal interactions* as characterized by so called *specific absorption rate (SAR)* while they completely neglect *informational interactions* [8] that show much more complicated dependence on interpersonal differences..

E. *Epilepsy*

During epileptic seizure chaos in the brain diminishes, neurons start firing in coordinated manner, fractal dimension of EEG-signal suddenly drops down (Fig. 5b).

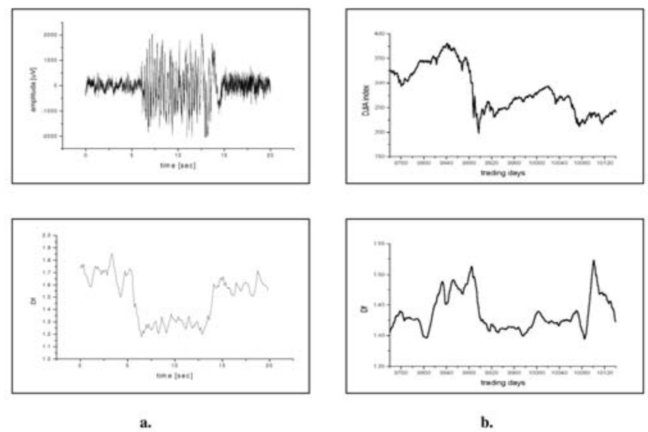


Fig. 5. Diminishing of D_f calculated from EEG unregistered during epileptic seizure (upper left), means diminishing of chaos in human brain. during epileptic seizure **(a.);** diminishing of D_f calculated from Dow Jones index from the period of 'Big Crash' of 1920's (upper right) shows striking similarity with epileptic seizure, despite of the huge difference in time scales. It does justify concept of **'**epileptic seizures in economic organisms' (**b).**

It is healthy to be chaotic! It is very interesting that in an 'economic organism' (and economists do like such personifications) one may observe very similar phenomena, usually named 'financial crisis'. We have shown that those are in fact 'epileptic seizures in economic organisms' [9].

Possibility of prediction of epileptic seizures based on $D_f(t)$ of EEG-signal as well as possibility of predicting economic failure based on fractal analysis of economic indices like Dow Jones needs further intensive investigations.

F. *Neurofeedback*

Neurofeedback for a physicist means exerting a conscious influence upon processes in the brain that normally are regulated unconsciously, based on some visualized quantitative characteristics of EEG-signal. Neurofeedback may be considered to be just a method of training that is assisted with an outer feedback pathway, e.g. a small computer displaying a game that may be controlled by EEG of the patient and at the same time calculating and displaying on the monitor some quantitative characteristics of the EEG-signal. In the biofeedback learning mode the patient learns to control brain activity in such a way that these characteristics of brain activity change in a way suggested by the trainer. When the training is finished the patient should be able to control his/her brain activities that are below awareness threshold with ‘willpower’ in a voluntary control mode i.e. without using outer feedback pathway, like one can recite a poem ‘from memory’ without looking onto text displayed on the screen while learning..

‘Classical’ neurofeedback is based on spectral characteristics of EEG-signal obtained by Fast Fourier Transform. But it is possible to use Higuchi’s fractal dimension of EEG instead of its spectral characteristics [10].

G. Assessment of Psychomotoric Tests

Psychomotoric tests - drawing figures on a computerized tablet according to the special prototype patterns – were performed by persons suffering with Parkinson Disease and persons undergone opiate replacement therapy. Due to the patient’s tremor both deviation of each drawing from the given prototypes and velocity of moving the pen fluctuate while drawing.

Fig. 6. shows mean Higuchi’s fractal dimension of the velocity of drawing, *FD* . It enables a simple assessment of the efficacy of surgical treatment of patients suffering with Parkinson Disease - of thalamotomy (**a.**) and of palidotomy (**b.**). While in both cases *FD* before surgery is smaller than corresponding *FD* of healthy persons and this differences are statistically significant, after surgery *FD* value of patients becomes nearly equal to that of healthy persons.

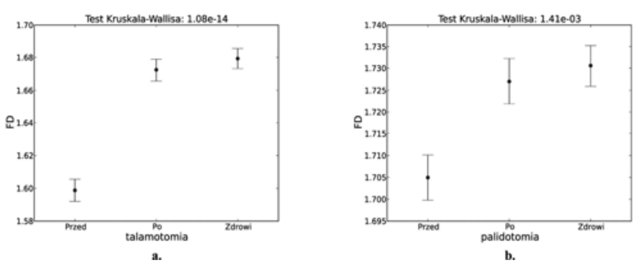


Fig. 6. Average D_f *(FD)* the velocity of drawing figures on the tablet during psychomotoric tests. *FD* values for persons suffering with Parkinson Disease before (‘Przed’, left bars) surgical treatment are lower than the values for healthy persons (‘Zdrowi’, right bars), but after (‘Po’, bars in the middle) surgical treatment – **a.** thalamotomy; **b.** palidotomy – the values rise nearly to those for control group of healthy persons. Kruskal-Wallis statistical tests show that the differences are statistically significant.

We have also assessed the same psychomotoric tests using another nonlinear method of signal analysis, so called Empirical Mode Decomposition (EMD) [11].

H. Assessment of Posturographic Signals

We assessed postural sway in elderly persons (mean age 71.5 ± 3.6 years) by calculating Higuchi's fractal dimensions of the center-of-mass (COP) and the center of foot pressure (COM) displacement signals registered in the form of time series. Postural stability declines with age; this decline seems to be accompanied by an increase of chaos in the postural signals as measured by D_f. Mean D_f of COM displacement signals was significantly smaller than this of COP. COP signal in the elderly seems to be more chaotic. Eyes closure resulted in an increase of the postural sway, accompanied by an increase of fractal dimension – elimination of the visual feedback univocally causes increased chaos in COP. Higher fractal dimension in the anteroposterior (AP) than in mediolateral (ML) direction indicates higher tendency for instability in AP direction [12].

Higuchi's fractal dimension method allows reliable evaluation of postural stability changes. It is useful and sensitive in evaluation of age-related decline of the postural stability and may also be useful for evaluation of pathological postural stability changes.

I. Seasonal Affective Disorder (SAD)

Therapy of some pathological states is based on *controlling chaos in the brain* by chemical drugs or by physical fields. So, measures of biosignal complexity such as Higuchi’s fractal dimension may be used for assessment of the applied therapy. For patients suffering of SAD a kind of phototherapy, so called *Bright Light Therapy* (BLT) is applied. Application of D_f for assessing BLT is interesting also because it illustrates the fact that the *speed of changes* of D_f may be of greater importance that the specific values of D_f.. Any short-lasting disturbance of a sensory stimuli cause changes in EEG-signal but shortly after it ‘relaxation’ occurs and the state that was before the disturbance is regained more or less rapidly. For example, opening or closing the eyes dramatically change EEG in particular on occipital electrodes (so called alpha-block). When an eyes-opening event occurs D_f of EEG-signal grows; then when eyes remain open D_f diminishes; then grows again when eyes-closing occurs; then when eyes remain closed, it diminishes again, etc. (Fig. 7).

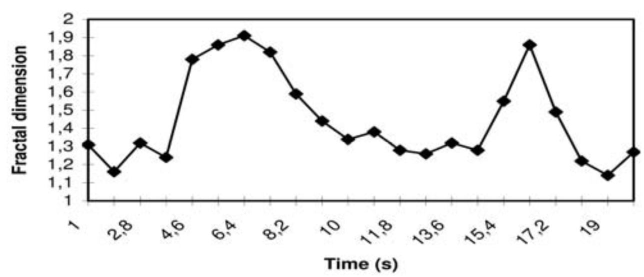


Fig. 7. Higuchi’s fractal dimension of 20 seconds EEG-epoch (P4-O2) with eyes-opening (in 4. s.) and eyes-closing (in 15. s.).

We analyzed EEG-data from SAD patients. collected just before and then 2 weeks after BLT. We have demonstrated that in patients suffering of SAD the 'relaxation' of D_f after eyes-opening/eyes-closing is slower than in healthy subjects ([13], cf. also [2])., but after BLT speed of relaxation becomes much closer to that of healthy persons. Assessment based on D_f is easy and quick and its results highly correlate with psychological assessment based on Hamilton Depression Rating Scale (HDRS).. We have also demonstrated that in patients suffering of SAD mean D_f of EEG-signal is smaller than in healthy subjects and that BLT makes the mean value of D_f in those suffering with SAD to increase .

IV. Other Examples of Using D_F in Medicine

A. Cardiology - Analysis of Heart Rate Variability

Living organism is '*spaghetti-like*'. Like pulling a single long thin string of spaghetti influence practically all other strings on the plate so a change in one system of the organism influence other systems, changing of one process in the organism influence other processes.

Interpretation of *electrocardiograms* (ECG) needs long specialized medical training. But from ECG one may obtain *Heart Rate Variability* (HRV) signal – the lengths (in seconds) of subsequent RR segments. It is even not necessary to register ECG since HRV may be also easily obtained from simple plethysmographic registration of pulse. $D_f(t)$ of HRV signal brings a lot of information of great importance also for Neurologists.

For example, using $D_f(t)$ of HRV signal registered during sleep it is possible to distinguish sleep stages Unlike in the case of EEG, fractal dimension of HRV reaches its maximum in deep-sleep stages 4. and 3. with mostly expressed parasympathetic input into heart rate control [14].

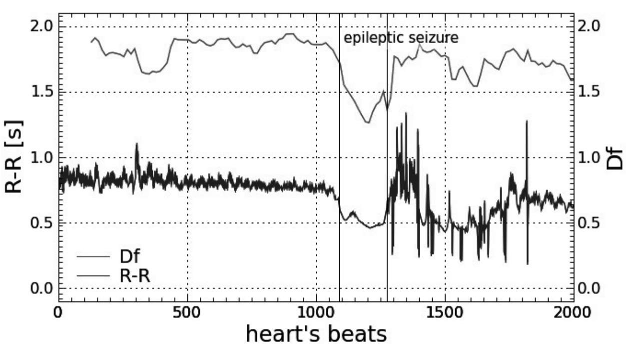
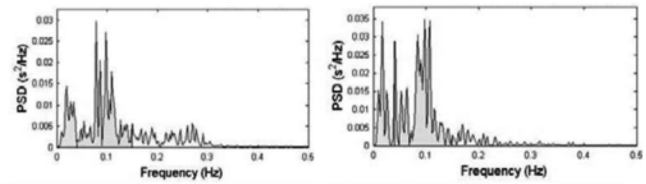


Fig. 8. Analysis of HRV of a person with post-ictal heart rate oscillations in partial epilepsy (bottom curve, left-side scale – RR of subsequent heart beats in seconds) (from [15]). Running *Df (t)* of this HRV signal (top curve, right-side scale) shows significant drop during epileptic seizure, localized according to info in Physionet by the data depositors based on simultaneous EEG recording (between heart beats 1090. and 1270.).

Also epileptic seizures may easily be detected in $D_f(t)$ of HRV signal. For example, when analyzing a case of a person with post-ictal heart rate oscillations from Physionet database [15] we found that $D_f(t)$ of HRV signal shows significant drop just during the epileptic seizure that had been localized by the data depositors based on simultaneous EEG recording as Physionet informs (cf. Fig. 8.).

Fractal analysis of HRV makes it possible to simply measure the person's *stress level* [16]. Fig. 9. shows frequency spectra (Power Spectrum Density, PSD) of HRV signals. For this purpose the signals should have been transformed from time domain into frequency domain by using Fourier transform. Frequencies observed in HRV, even those named 'high frequencies', are in fact lower than 0.4 Hz, i.e. much lower than frequencies observed in EEG-signal. Stress used to be characterize by the ratio of total power of low frequencies, *LF ,* to the total power of high frequencies, *HF.* This needs numerical integration of the spectra.. We have analyzed original HRV signals in time domain using Higuchi's fractal dimension. that is a much simpler and quicker way of analysis. We have found that unlike *LF/HF ratio* in high stress D_f of HRV-signal decreases (Fig. 9.).

More about HRV analysis using Higuchi's fractal dimension in [11].



Frequency Band	Peak (Hz)	Power (ms²)	Power (%)	Power (n.u.)
VLF	0.0195	232	17.9	
LF	0.0781	719	55.4	67.5
HF	0.2695	346	26.7	32.5
LF/HF			2.078	

a.

Frequency Band	Peak (Hz)	Power (ms²)	Power (%)	Power (n.u.)
VLF	0.0176	347	20.6	
LF	0.0977	1141	67.5	85.0
HF	0.1699	201	11.9	15.0
LF/HF			5.667	

b.

Fig. 9. Analysis of HRV signal of a person in low and in high stress. Spectral analysis shows that when the level of stress increases then the ratio of low frequencies (*LH*) to high frequencies (*HF*) increases while fractal dimension of the HRV signal, D_f , decreased. Level of stress was independently determined by analyzing person's blood for 'stress hormone' - cortisol.

a. Low stress - D_f= 1.62; **b.** High stress - D_f = 1.49

B. Psychiatry - Assessing Effects of Electroshocks

Electroconvulsive therapy (ECT) is a successful treatments for depression and other mental disorders. We have analyzed non-stationary EEG signals measured on frontal electrodes of patients who have received ECT. The effects of ECT on the patients are monitored with EEG. EEG evoked by ECT (ECT-EEG) exhibits specific patterns with four phases but there are differences between individuals. $D_f(t)$ may be a help for clinicians to simplify analysis of ECT-EEG (Fig. 10) and to find new properties not identified by other methods. For example, it was found that psychotic depressed patients show higher increase of $D_f(t)$ in phase 4. in comparison with bipolar depressed patients, so indicating a difference in neurodynamics between two groups [17].

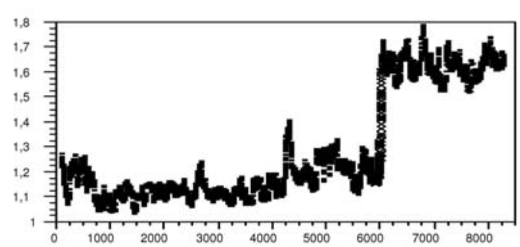


Fig. 10. Higuchi's fractal dimension of ECT-EEG on Fp1 clearly indicates transition from phase 3. to phase 4. not easily identified in the signal itself nor by other methods of analysis.

C. Anesthesiology - Monitoring the Depth of Anesthesia

So called *bispectral index (BIS)* used in the BIS Monitors (Aspect Medical Systems, Newton, MA, USA) is commonly accepted as a measure of the depth of anesthesia, but the algorithms used in BIS Monitors are not in public domain.

We have proposed a new method of monitoring the depth of anesthesia by assessing complexity of EEG-signal based on Higuchi's fractal dimension [18].

In addition to registration of EEG-signal and BIS the depth of anesthesia was continuously tested and classified by a specialist-anesthesiologist to six **OAA/S** levels (*Observer's Assessment of Alertness and Sedation*); patients were judged to be conscious if the OAA/S score was between 3 - 5 and unconscious if the OAA/S score was less then 3. Example of our results is shown in Fig. 11.

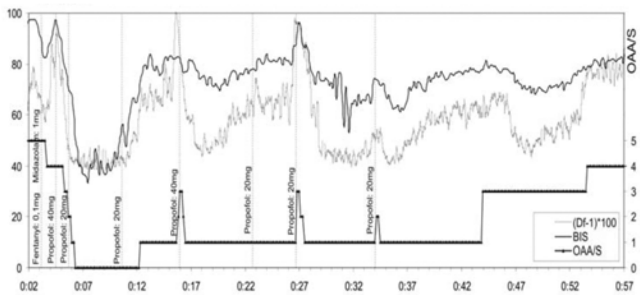


Fig. 11. In this case anesthesia was controlled according to BIS (target BIS value between 60 and 80) with intermittent boluses of propofol. At 16. and 27. minutes sedation was lightened to level 3 in OAA/S score (black step curve, right-side scale). At those moments fractal dimension of EEG (lower light-gray curve) drawn here as *$(D_f$-1)*100* to be easily compared with BIS index (upper dark-gray curve), (cf. left-side scale), rose rapidly to rich the highest value. BIS increased only once (at 27. min) while at 16. min. it remained practically unchanged. Awakening during surgical procedure and at the end of it can be predicted by rise of *$(D_f$-1)*100* towards its highest value.

It seems that D_f of EEG-signal despite of its simplicity is even better suited for monitoring of the depth of anesthesia and sedation than BIS index.

V. 'NORMAL VALUES' IN MEDICINE - PROTOCOLS MAY LEAD TO SERIOUS ERRORS

Human organism (and human brain in particular) is a highly complex nonlinear systems (cf. [2]), and that is why *standardized approach based on 'stiff' protocols may lead to serious errors of judgement.*

There are differences in defining 'normal' ranges even between quite reliable sources. For example, in Medline one may read: 'Normally, the ICP [Intracranial Pressure] ranges from 1 to 15 mm Hg', but other sources give ranges like 8 to 18 mm Hg; anyway, what for one person is quite high ICP for the other may be quite low (cf. [22]) and if this person was treated according to a protocol that said 'decrease the patient's high ICP' he/she might die.

A. Hormesis

A nonlinear effect called *hormesis* manifests itself in a *nonlinearity in dose-response behaviour*, like stimulatory effects caused by low doses of inhibitors (*β-curve*) or inhibitory effects caused by low doses of stimulators (*U-curve*, Fig. 12.). The best-known hormetic-type effects are the stimulatory effects of alcohol, caffeine, or nicotine, all of which are toxic at high concentrations. Hormetic effects concern not only chemicals but physical exposure as well. For example, adaptive and stimulating effects of ionizing radiation occur at near natural doses - this disagrees with linear, no-threshold hypothesis on the dose-effect relationship.

Commonly used statistical tests are not optimized for use with such data - the assumption of monotonicity is implicit in these tests and results in a reduction of the possibility to identify changes in an unanticipated direction.

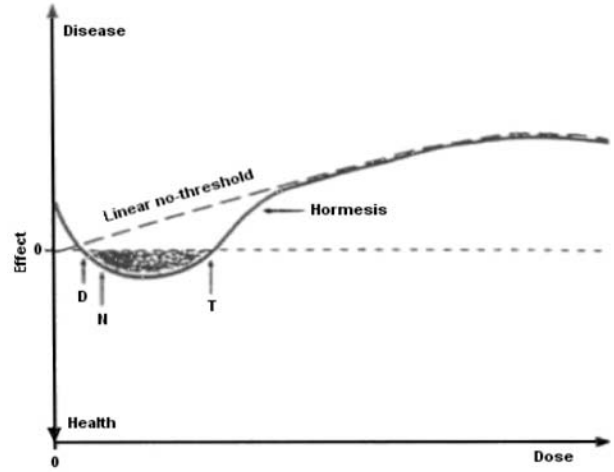


Fig. 12. Hormetic dose-response U-curve (after [24]). Deficit of an agent (doses less than D) causes deficiency symptoms; small doses (between D and T) are vital for good health (shaded area), doses higher than T cause toxic or other harmful effects. Dotted line represents linear no-threshold dose-effect relation that is often implicitly assumed by those researchers who are '*infected with Human Linearity Virus'.*

Ignoring hormetic responses in the analysis of data, in particular using models that cannot accommodate potential effects of hormesis may lead to biased estimates..The problem here lies again in *impossibility to define norms.* What for one person is 'normal' i.e. it is a small dose that have positive effect on this person, for another person may already be a very large dose, a cause of illness or even of death.

B. Sensitivity to Electromagnetic Fields

Electromagnetic fields (EMF) generated by different technical devices in our environment are not without an influence on our health. So called '*norms of exposure*' to EMF mislead even Medical Doctors since they are based only on *thermal interactions* as characterized by so called *specific absorption rate (SAR)* while they completely neglect *informational interactions* [8]. A living organism is an *open system,* pumped with free energy from biochemical reactions, similarly like a TV-set is pumped with free energy from electrical outlet. EMF that interact with the antenna of a

TV-set bring extremely low energy; what EMF waves bring is *information* that influence the system and may cause either meaningful or just noisy images to show up on the screen.

There are no norms that assess information effects of EMF on human organism. Identical exposition to EMF of identical intensity may show very different effects in different persons, and even effects in the same person may differ depending on the person's psycho-physiological state. Living system are highly nonlinear and operate far from thermodynamic equilibrium, that is why methods of Nonlinear Dynamics and Chaos Theory [24] are much better suited for assessment of EMF influence than 'classical' linear spectral methods.

Even European Parliament stressed this important fact in a report (cf. [25] pp. 23-24) : 'Future research sponsored by the EC, should incorporate the following recommendations: (…) That systematic investigation be made of the influence of different kinds of pulsing (of real phones) on the human EEG, and ideally on the MEG, and of *whether any observed changes in power spectra are correlated with changes in the level of deterministic chaos*'.

The Authors of [26] did claim that using spectral method they had demonstrated that certain NPD (*neutralizing protective device*) .really neutralizes negative influence of EMF generated by cellular phones.. When we analyzed the same EEG-data using Higuchi's fractal dimension one has not only shown that for majority of users (7 out of 8 analyzed cases) the NPD has practically no effect, but one may also point at one person out of 8 who is more sensitive (hypersensitive) to EMF [8] (Fig. 13.). About 12% to 18% of population may belong to a high-risk (hypersensitive) group of cellular phones users, at least of certain phone models, and for those persons NPD may be a matter of choice.

The methods used in research as well as interpretation of the results depend a lot on who is financing the given research [27]-[29]. That is why independent basic research financed by public money are extremely important.

C. Reference and 'Normal' Values in Medicine

Absolute health does not exist – health is necessarily a *relative* concept [30]. This implies that the condition of an individual must be interpreted by comparison with some reference data. The decision making may be *computer-assisted* but as we have just demonstrated the rules based on the probabilistic and statistical techniques, as they are used by computerized expert systems, may be very misleading.

The term *normal values* as it is often used in Medicine is roughly equivalent to *reference values obtained from healthy individuals* [30]. But who is *really healthy*?

The best reference values are the previous values from the same subject. Individual values also undergo changes. For example concentration of Prostate Specific Factor, *PSA* , increases with aging. But a PSA value out of the 'normal' limits does not raise the alarm of prostate cancer unless it has risen from the previous value in a rather short period.

VI. CONCLUSIONS

Nonlinear models and nonlinear methods of data processing are much more appropriate in Biomedicine than 'classical' linear methods that may lead to very misleading results. Quantitative descriptors supplied by Physicists, adapted from Nonlinear Dynamics and Deterministic Chaos Theory, in particular fractal methods of analysis in time domain, may help in better assessment of various spontaneous or evoked, normal or pathological functional states of the brain (cf. [20], [21]) and in assessing impact of applied therapies [11]. It is interesting that the same methods may also be adapted for socio-economic system analysis to reveal different 'physiological' and pathological states of society and government.

Living organisms are complex nonlinear systems and the human brain is the most complex system we know. As stated in the above mentioned European Parliament report (cf. [25] p. 14): 'Difficulties sometimes experienced in attempts to independently replicate certain frequency-specific non-thermal effects *are actually to be expected,* in consequence of the highly non-linear, non-equilibrium nature of living systems, whereby even the slightest differences in the physiological state of the biosystems used and in conditions obtaining in a particular experiment can, in consequence of deterministic chaos, assume singular importance'.

And this is exactly the reason why in Medicine any 'norm' is only of very relative importance. *In Medicine two plus two not always equals four* [31] and that is why there is no alternative to Personalized Medicine provided by really well trained Medical Specialist (cf. [3]).

It is the personalized approach to diagnostics and the treatment tailored to each individual's biological and psychological personal profile that should be *the norm* in contemporary Medicine, in everyday medical practice

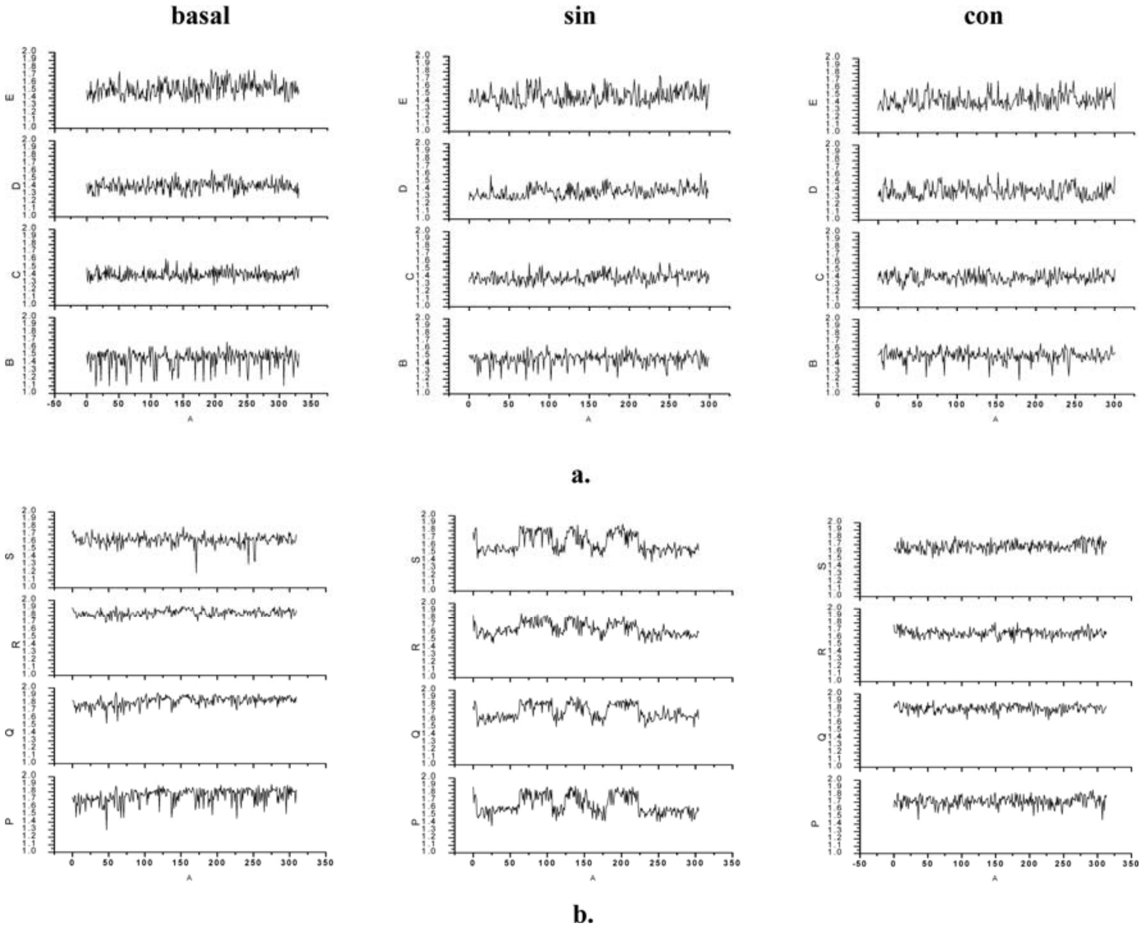


Fig. 13. Higuchi's fractal dimension of 300 sec. long epochs of EEG-signals. **a.** of a person who does not show sensitivity to EMF of the cellular; **b.** of a person who may be (hyper)sensitive to EMF. In the columns, from left to right, respectively: **basal** – phone at place but not in use; **sin** – phone in use, without NPD; **con** – phone in use, with NPD. EEG was registered on 4 channels respectively (upside down): T6-O2; T4-T6; F8-T4; Fp2-F8. For the sensitive person Higuchi's fractal dimension, $D_f(t)$, shows characteristic 'saw-teeth' pattern (cf. Fig. 4.d.) when cellular phone is in use without NPD (EEG-data thanks to J.L.Bardasano and I.Gutiérrez, Department of Medical Specialties, University of Alcalá, Madrid, Spain, cf. [26]).

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