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Computer Methods of Investigation of Ultralow Doses Effects in Biomedical Applications

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Abstract **-** Investigation of effects of substance (or radiation) ultralow doses on biological systems is a problem of significant importance. Numerous researches in natural sciences, especially in physics and biophysics of living organism, resulted in making a model of ultralow doses effects. These effects are based on the special structure of water in living cell (fractal crystals) and the mechanism of energy transfer and transformation in biomolecule chains. In the model the transfer process is fulfilled by soliton that demonstrates a transformation of incoherent chemical energy absorbed by a biopolymer into a coherent electromagnetic form and may have a resonance with the dielectric surrounding the biopolymer. As for now it is practically impossible to observe this effect in a living organism directly. But we can register changes in an organism states using data of blood analysis or thermal imager. Considering biological system as a complex dynamical system we assume that images of a process in an organism obtained in different instants of time are phase portraits of the process. This leads to application of mathematical and computer investigation methods to studying biological processes. In this paper we describe the application some mathematical methods to analyze biomedical preparations images and obtain some numerical characteristics of the process under investigation. We also discuss a method of exploration of the influence of low doses of magnetic fields in magneto therapy devices on a human organism.

Keywords**:** Ultralow doses, Digital images, Dynamical systems, Stationary process, Fractal analysis, Mathematical morphology, Magneto therapy.

1. Introduction

It is well known that any external factor (physical, chemical, etc.) acting on an organism in one way or another changes the organism functioning. As this takes place, a specific answer of the organism appears for any value (dose) of the action. Ultralow doses are used both in classical (acupuncture, electrophoresis) and homeopathic medicine, hence from this point of view the separation medicine on allopathic and homeopathic is artificial and conditioned by historical and economic reasons. As far as application of large doses of medicines may lead to side effects, many specialists suppose that low and ultralow doses provide more delicate treatment.

Numerous researches show that within the scope of the paradigm of classical medicine a study of ultralow doses effect is rather difficult. Recent advances in natural sciences, especially in physics, offer a clearer view of how these mechanisms work. Investigation in this area may promote considerably to the progress of so called evidence-based medicine.

Many distinguished scientists made a contribution to the forming common approach to the study of complex biological systems. It was Boltzmann (1939) who made an effort to reduce the biological evolution theory to thermodynamics and chemistry of 19 century. He connected micro processes in an environment with its macro state and proposed to consider an integral characteristic of a system —

entropy. Prigogine (1964), who investigated nonequilibrium processes in open systems (supposing that any system has an environment), also considered entropy as a system characteristic. Russian biologist Shmalgauzen (1938) and physiologist Anokhin (1963) asserted that the main property of an organism is the integrity that cannot be reduced to the sum of its elements. The founder of homeopathy Hahnemann (1835) also considered a human being as a whole system and developed his treatment methods (based on ultralow doses application) in accordance with this approach.

System study of biological systems unites theoretical results and applied investigations, and allows us to consider both qualitative and quantitative characteristics of common principles of systems functioning. That leads to active using both mathematical and computer modeling. The necessity to apply system method for comprehension of mechanisms of ultralow doses effects is substantiated in (Horouwitz, 2013).

When studying ultralow doses effects we can use theoretical results, namely achievements in physics, that led to the explanation and substantiation of these effects. They are based on a special structure of water in living tissues and the method of energy transfer in biomolecule chains. For complex processes in living tissues it seems practically to be unreal to make a mathematical model. We have to solve so called inverse problem: given a system functioning results (or measurements) to analyze the system behavior, where "to analyze" means to obtain some characteristics and interpret them. To analyze the results of ultralow effects one can use bio tests (for example blood analysis, thermal imager data). It is the analysis of digital images that opens up possibilities to apply mathematical and computer methods to obtain comparative characteristics and classification signs of the images.

In the paper we discuss the results of application both mathematical and computer methods to obtain numerical characteristics for different classes of biomedical preparation images.

2. On an Exploration of Ultralow Doses Effects

In physics by low doses effects (or low signals) is meant both a measure of an action on an object and the value of the answer of the object. In classical sense the notion "experiment" means a purposeful action on an object that answers by a signal, and this signal should be measured. In this case it is implicitly assumed that when measuring only one acting factor is registered.

It should be noted that any effects, both low and ultralow, generate in a system a complex answer. But for low effects in the majority of cases the components of the answer are composed to a resulting signal, whereas for ultralow effects it does not take place.

In this situation we should estimate a change of a system state integrally and use bio tests as indicators of such changes. The changes in bio test states really happen, are observed and may be experimentally registered.

2. 1. Ultralow Doses of Substance (Hyper Weak Solutions)

The properties of so called hyper weak give us an important example of complex results of ultralow doses effect. Many theoretical and experimental investigations performed by Szent-Gyorgyi (1957), Burlakova et al.(2008), Konovalov (2012), Del Giudice et al.(2009), Ling (2001) and many others allow us to formulate the following:

• A set of biologically active substances, many of which are used as medicines, demonstrate in hyper weak solutions special properties that they have not in more concentrated ("classical") solutions. The answer of an organism on a drug substance action when consecutive decreasing its concentration is nonlinear and non-monotonic: for ultralow concentration the answer may increase again. These properties are called "bimodal biological effect".

• These substances in hyper weak solutions show special physicochemical properties and form so called nanoassociates of rather large size (up to 200 nm).

• In addition these properties are observed only if solutions are saved no less than 18 hours in the magnetic field of the Earth, and not observed if the solutions are in a screening container.

• It is the magnetic field of the Earth that determines special properties of hyper weak solutions and acts the organizing role in all the structural processes concerning to water.

The mechanism of ultralow doses effect is rather complex and at the moment there is no complete theoretical results. At the same time we should note, that a model explaining this phenomenon was described by Russian physics Gall (2009, 2010).

2. 2. Ultralow Doses of Electromagnetic Radiation

In spite of a wide range of papers concerning the area of the influence of electromagnetic radiation on living organisms it is difficult to specify clearly its positive and negative effects. We can find a lot of references in the review Cifra et al. (2011), where experimental results concerning both electromagnetic radiation influence and intracellular interactions are discussed. In practice low frequency magnetic fields are used in magneto therapy, and in many cases lead to positive results in treatment. Such a therapy agrees well with traditional medicine methods.

At the same time there are no common rules to fit parameters in various magneto therapy devices, because, as it was mentioned above, the mechanism of action of ultralow doses both physical fields and medicines on living organisms is rather complex and not sufficiently studied. One of perspective approach to parameters choice ensuring maximal medical effect was proposed in (Efremov, 2006). The method is based on fundamental facts of the biophysics of sensory systems which describe the answer of a bio system on external exposures. The author also considers an inspection method of the patient health.

Hence at the moment the main method to study a weak magnetic field effect on a living system is the experimental one. For some classes of magneto therapy devices, when magnetic field is produced by coils, one can use a mathematical model. Magnetic induction is calculated, results are visualized. By changing parameters (current intensity, distance between coils) a physician may compare treatment results and visualization of a magnetic field distribution and select an appropriate regime.

3. Practical Exploration

It should be noted that in the majority of cases in studies of complex biological system we cannot count on a mathematical model making. Hence we have to follow practical methods of investigation — experiments and measurements. Modern technologies put forward a wide spectrum of high-resolution hardware to measure and register processes elapsing in biological systems. The results of measurements may be obtained as digital images which are classified and analyzed by precise mathematical methods. The revealing an image structure and characteristics may considerably help a physician in diagnosing.

In analysis of such images statistical, texture, multifractal, morphological and spectral signs and their combinations are used. Many of these characteristics are invariant relative to wide class of image transformations, such as rotation, change of illumination, scaling. If there is a mathematical model of a process under investigation (described by a system of equations), one can use numerical methods to find a solution. All these methods may be applied to elaborate modern software and hardware instruments in investigations and treatment when using homeopathic medicines and other methods of evidence-based medicine. Now we consider examples of application of various mathematical methods.

3. 1. Mathematical Modelling of Low Frequency Magnetic Field

The study of the action of low frequency magnetic field in magneto therapy devices is one of the most important problems in clinical practice. The papers (Ampilova et al., 2013a, Kudrin, Dimitrov 2013a, Kudrin, Dimitrov 2013b) are devoted to the construction of space configuration of magnetic field for different configurations of the coils. In that model distances between the coils are long enough and the mutual induction is not taken into account. The obtained numerical results and their visualization may be used to estimate the effectiveness of clinical procedure: changing the parameters of configuration a physician may choose a more appropriate regime.

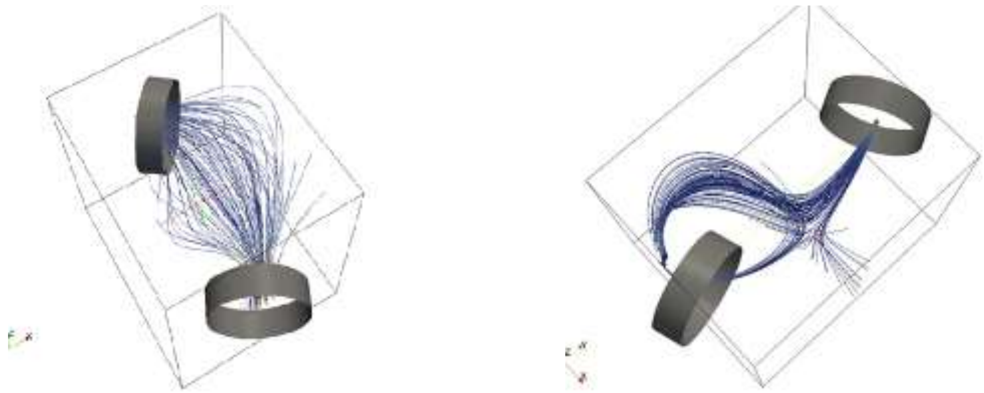


Fig. 1. Vizualization of spatial configuration of magnetic field for given pairs of coils.

3. 2. Mathematical Modelling of Diffusion Processes by Stationary Processes on Graphs

A method of a classification of images concerning to a substance propagation process was proposed in (Ampilova, 2013). The image is considered as a lattice formed by pixels (i, j) of given intensities $0 < I(i, j) < 256$. Then an oriented graph corresponding to the image is constructed in the following way. Every vertex (i, j) has the weight $I(i, j)$; every vertex (pixel) is connected with N neighbours, such that for a given vertex (i, j) all out coming edges have the value $I(i, j)/N$, for boundary vertex — $I(i, j)/k$, where $k=N$-1 or N-2 for N=4 and $k=N$-3 or N-5 for N=8. The constructed flow is normed such that sum $I(i, j)$ equals 1. Hence we obtain Markov chain on the graph: for every vertex its weight equals sum of weights of outcoming edges. Denote the initial distribution on graph edges by p_{ij}. Our purpose is to find such a distribution u_{ij} that the flow on the graph be stationary: for every vertex the sum of weights of incoming edges equals the sum of weights of outcoming ones. It is well known that such a problem has a solution if there is a cycle on a graph; the solution may be obtained by the Sheleihovsky-Bregman method (Bregman, 1966). Moreover, this solution minimizes weighted entropy $g(u) = -\sum_{i,j} u_{ij} \ln {}^{p_{ij}}/_{u_{ij}}$.

It is weighted entropy that is used as a classifying sign when images concerning to different doses of a substance are analyzed. In fact, weighted entropy may be considered as a time that is required for a distribution process to achieve a stationary state: the more concentration the more this time. On the Fig.2 pharmacological solution of Ag obtained by atomic-force microscope for different concentration are shown. They correspond to (from left to right) zero, small and large concentrations. Weighted entropy is equal to 0.0000025, 0.000013 and 0.000043. It is easy to note that the proposed method separate images with zero concentration from others.

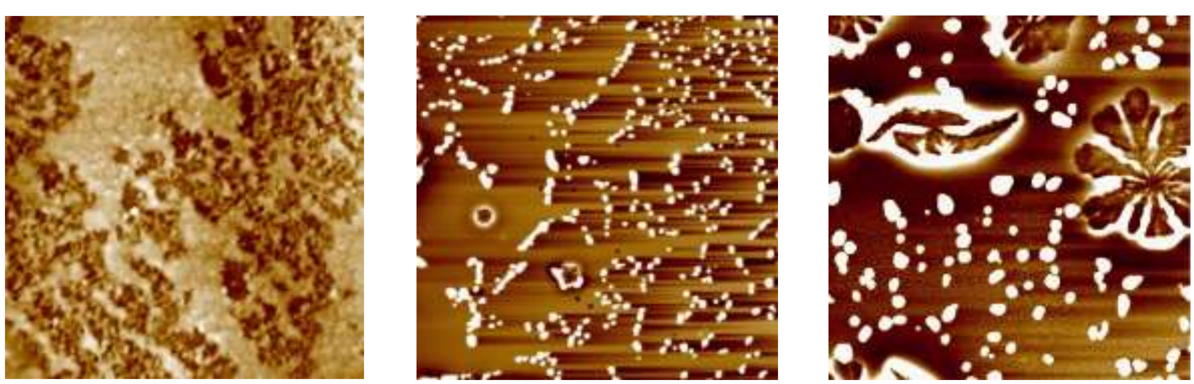


Fig. 2. Images of pharmacological solutions of AG with different concentrations.

3. 3. Fractal Analysis Methods

Methods of fractal and multifractal analysis are widely used for various types of images. Considering an image as the phase portrait of a complex dynamical system we can use for its description multifractal formalism as a statistical characteristics. Multifractal formalism relies on the fact that highly nonuniform probability distributions arising from the nonuniformity of the system often possesses rich scaling properties such as self-similarity. Hence we can associate a characterization of the fractal properties of a measure with the nonuniform distribution. The multifractal formalism describes the statistical properties of these singular measures in terms of their singularity (multifractal) spectrum or their generalized dimensions (Regny spectrum). The generalized dimensions were introduced earlier than multifractal spectrum and they are easier to compute than multifractal spectrum.

We applied both methods to classify images of histological preparations, connective tissues, bone tissue and many others (Ampilova et al., 2013b). To classify pharmacological solutions of Ag containing different (low) doses of the substance we used Regny spectrum (Ampilova et al., 2011). Regny spectra for the images on Fig.2 are shown on Fig. 3.

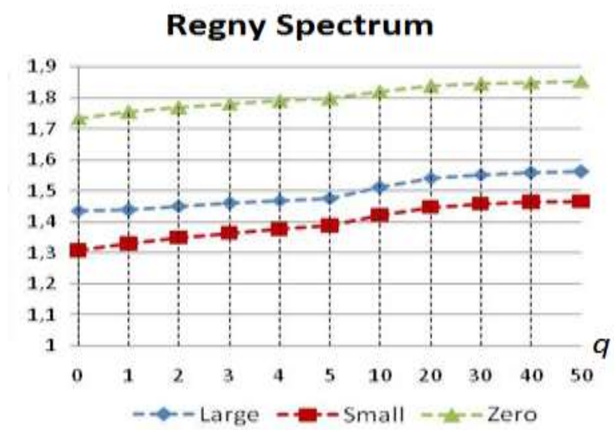
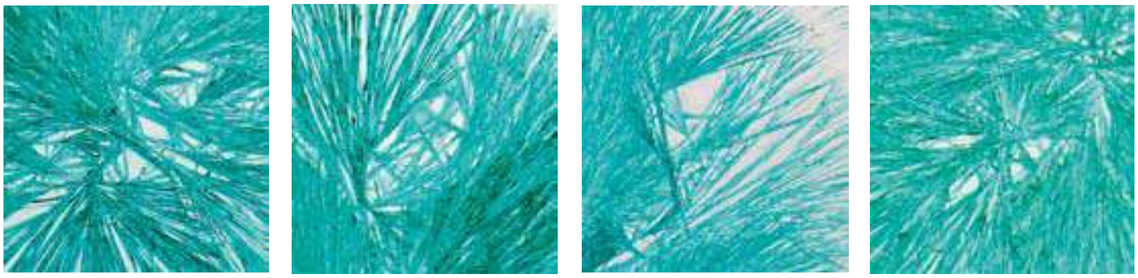


Fig.3. Regny spectra for images of pharmacological solutions of AG with different concentrations.

3. 4. Mathematical Morphology

The method of sensitive crystallization was developed by Pfeiffer as early as in 1930h (Pfeiffer, 1935), but still is pioneer one. The method is based on addition of whole blood (or plant extracts) to a solution of cuprum chlorides. The foundations of the method and a systematics of experiments with blood crystals are described in detail in (Selawry A., Selawry O., 1957). In (Selawry, 2011) the author studied influence of metals on human being and assumed that results of the crystallization may be indirect proof of malfunction of metallic processes in a patient blood. The method also results in defining malfunctions of organs and pathological processes in organism. For blood the crystallization by cuprum chlorides is a sensitive morphological test. It seems the blood formulation (low doses of some substances) defines the type of crystal. This method is very important in homeopathy. Currently the method has attracted considerable interest of many scientists. Waldburger (2013) assumes that crystal structures demonstrate a dynamic of processes in human organism and discusses perspectives of blood crystal analysis.

The application of rigorous mathematical methods to different kinds of blood crystal images allows us to extract many features such as regular areas, cavities and structures. Typical forms of crystals corresponding some organ malfunctions (Waldburger, 2007) are shown on Fig.4. In (Soloviev et al., 2012) such images were classified by the methods of mathematical morphology.



a b c d

Fig. 4. Types of images of blood crystals: a) hole structure of crystals – typical for degenerative processes; b) hollow form of the crystal, benign tumor; c) hollow form of the crystal with transversal structures, malignant tumor; d) crystallization in the star form with hole structure, which is typical for chronic inflammatory process.

On Fig. 5 blood crystals of 3 patients are shown. All the images indicate signs of chronic inflammation. Specific forms characterizing acute states are not found.

Fig. 5. Images of blood crystals having various signs of chronic inflammation process.

4. Conclusion

Recent advances in physics, chemistry, biology, mathematics, computer sciences and their applications resulted in the substantiation and explanation of the mechanism of ultralow doses effect. Though now it is practically impossible to observe this effect in a living organism directly, we can use different forms of bio tests: digital images of biomedical preparations and numerical data obtained both in practical experiments in magneto therapy devices and results of mathematical modelling of magnetic field distribution. The application of mathematical and computer methods of investigations allows us to obtain characteristics of biological system states when acting by low and ultralow doses of medicines and other external factors. The design of methods of acquisition of living system images on below-cell level is one of the most important problems for future explorations.

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