Y.N. Makov

ULTRASONIC NANOMEDICINE: NEW DIRECTION, NEW POSIBILITIES TREATMENT TECHNOLOGIES

Department of Acoustics, Faculty of Physics,
Moscow State University,
Russia, 119992 Moscow, Leninskie Gory
Tel.: (495) 939-31-60;
E-mail: yuri_makov@male.ru

*On the one hand the modern possibilities of ultrasonic application in medicine and his action on the cell level and on the one hand the observed active development so-called NANOsciencies and NANOtechnologies for purposeful research and utilization of the nanoscaled distnctive objects (atoms, molecules, reference complexes from them) yield good reason to speak about the forming of the special interdisciplinary scientific direction «**ultrasonic nanomedicine**». The interaction of the participated in process principal objects with the dimensions that exceed greatly of the nanoscales (the micron sizes of the cells and millimeter wavelengths of the « medical ultrasound»), nevertheless, generates just nanoscale processes solving medical problems on the cell level.*

The qualitative perfecting of any field of the fundamental science is largely determined, on our view, by the following three processes: i) by the assimilation « as a whole » of the more higher level of complexity of viewed problems (for example, by the transition from the analysis of the linear problems to the analysis of nonlinear processes), ii) by the expansion of boundaries of the spatial sizes and/or the time scales(just as in the decreasing side so in the increasing side), iii) by the scientific « inter-beneficiating » under the formation and development of the interdisciplinary (boundary) scientific directions. These processes so potentially are relevant in themselves, that they not only determine the development of the individual, already existing, scientific directions, but also provoke appearance of the new scientific disciplines, areas, etc. So already mentioned assimilation of the nonlinear problematic in all partitions of physics with the unity in the approaches, methods and even the equations yields the basis to speak about the forming of the presumptive scientific discipline - «nonlinear physics» [1]. With other, common for many natural sciences, process of the active research of the «specific» properties of the nanoscaled objects (atoms, molecules, reference complexes from them), with the creation of the nanoarchitectural principles and the governing of these complexes are connected the modern tendencies in forming and development of the so-called NANOsciences and NANOtechnologices. It is interesting to mark, that the rather short (two decades) history of the appearance (birth) and making of this new field is determined not only (and even, it is not so much) by two important scientific achievements, first of which is a making of a scanning tunnel microscope (G. Bennig, G. Rohrer, 1982) and scanning atomic-powered microscope (G. Bennig, K. Kuatt, K. Gerber, 1986), marked by the Nobel premium in 1992, and the second - discovery of the new form of the carbon existence as fullerene (H. Kroto, J. Health, S. O'Brien, R. Curl, R. Smalley, 1985), also is marked by the Nobel premium of 1996, but in the much greater degree, with the realization and understanding of the potentials (first of all, in applied usage), that open in the use of the nanostructures with requisite compositions, properties and functions. Just it is illustrated in full measure by the book [2], whose moment of the appearance gave actually the beginning of the existence of the concepts «nanotechnology», «nanosciences» and corresponding new scientific/applied direction *). In the absence of any mathematical, physical or chemical formulas, build-up and analysis of any concrete models this transactions, this book was given the conceptually - philosophical and futurological understanding of this new scientific field, and marked really of its appearance and has became the peculiar «manifest». Also here obvious example of the efficiency of the well-timed definition and «fastening of the status » of new scientific field is too seen here, that has allowed to attract attention to it and to integrate of the efforts of the specialists in different sciences,

*) The idea about «nanotechnologies» was included in the report «There's Plenty of Room at the Bottom. An invitation to enter a new field of physics" (1959) by R. Feynman.

which have provided the big progress in the short time. The formed by this means scientific/applied field of the nanotechnology is essentially interdisciplinary, where the «professional» opportunities and interests of physics, chemistry, biology, electronics, robotics etc are joined. At the same time, the inverse process is watched also, when under the influence of a new common direction the orignal subsections in traditional sciences are arisen. So, in resent years the progects of the future, directed on «tracing, rectifying, constructioning and check of biological systems of the homo sapiens on the molecular level utillizing designed nanodeices and nanostructures» [3] (this is accepted as the canonical definition of the **nanomedicine**) are very actively considered. The orientation of this definition (and corresponding design projects) on availability special nanorobots for the realization of the medical technologies compel to correlate all this on the future, that is adjusted with the conventional prognoses. However, yielding more adequate, on our view, **the definition of nanomedicine as the system of scientific methods and practical technologies allowing to reach of diagnostic and medical effects on the nanoscaled (molecular) level**, is possible already to sertify the today's accessibility of the nanomedical technologies in practical using with the cognizance that the ultrasonic action on the tissue and through them - on separate cells is played the considerable role and this actioning process is the nanoscaled. It yields the basis for the the definition and fixation of "**ultrasonic nanomedicine**" as the special bracing of the nanomedicine. On the one hand this reflects the realistic today's possibilities and successes in this field (ultrasonic medicine on the nanoscaled level) and on the other hand this new name and new direction are the preffered area for the attraction and the integration of the efforts of the specialists in the different fields for the active progress of the this new scientific direction joining the acoustics and nanomedicine capabilities. Before the substantiation of this new «terminological bunch» in more details, we shall make two important in principal notes. Firstly, the combination of acoustics with nanotechnologies goes on two directions: i) by the degrease of used ultrasonic wavelengths up to micron and smaller scales (for example, in a ultrasonic microscopy) and in this case speak about «nanoacoustics» [4], ii) the other direction is the processes of action of ultrasonic waves of «standard» scales on the proportional objects with the resulting effects on «nanolevels». Just this second direction is characteristic for defined by us «ultrasonic nanomedicine», where the using of the transiting through tissue ultrasonic waves with a millimeter or greater wave length for action on separate cells and their components of the micron sizes result to nanoscales processes for the diagnostic and therapeutic effects. The indicated action can be direct (ultrasonic wave - cells) or through «intermediaries» like the bubbles, molecular structures, specially inject into organism, etc. The second note concerns the next relevant fact, that already in «canonized» nanotechnological projects for future [2, 3] the major functions of «communications (connection) and telemetries» are imparted to acoustics.

Speaking about the new pithy concept and corresponding new scientific/applied direction «ultrasonic nanomedicine», it is necessary all time to mean, that in all conventional for today ultrasonic applications in medicine the any kind of the ultrasonic action (at the expense of the different mechanisms) on the separate cells takes place. The underlining of it is important because now practically all possibilities of using of acoustics in medicine are analyzed by the consideration of the «standard» physical factors (the conditions of the acoustic waves propagation including the nonlinear effects, thermal processes etc.) in some modeling «continuous medium», which one exchanges the actual tissues and do not take into account the actual cellular texture and possible effects of acoustic waves activity on the cell level.

In view of the fact, that the real basic objects of the action are the separate cells (healthy or pathologically transformed, e.g. cancerous), basic structural components of cells (first of all, the biomembranes), different bacteria, molecular and gene structures, and the role of the«instruments» of action is played by the ultrasonic waves which are capable to propagate in tissues on sufficient distances (that determines their wave length $\geq$ 1мм), and some «secondary» mechanisms of action (for example, cavitation), we shall give a comparative scale of reference scales for these objects participating during interaction (see. Fig.1).

As is known, natural boundary of each cell is the cellular biomembrane, which one except for protective functions ensures exchange processes with «external world», and consequently the any

structural, functional etc. changes of a membrane by an essential fashion have an effect for vital activity of the cell.

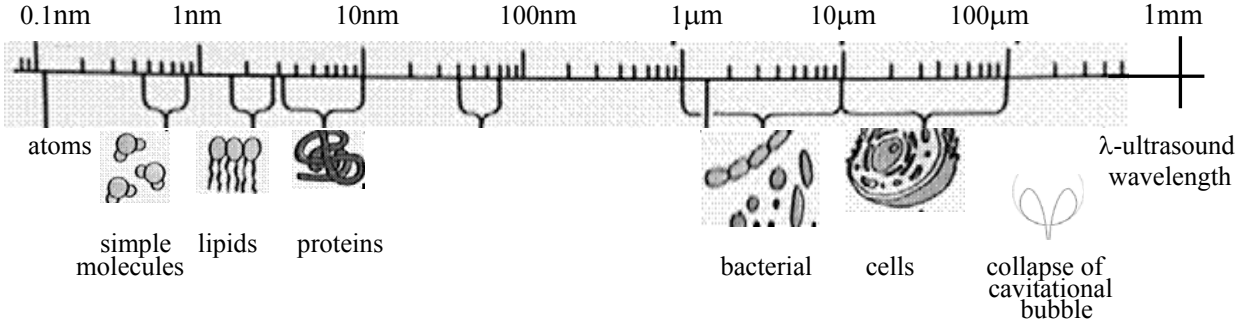

Fig. 1. Typical sizes of the objects participated in the interaction "ultrasound – cells and cellular structures"

Geometrically and physically the ultrasonic action on a cell, first of all, is the action on a biomembrane and, as consequence, are the influences on full cell. The important features of a cellular membrane are its essential two-dimensions (under the typical sizes of radius by a restricting membrane of cell are 5 - 20 microns and its areas are 300 - 5000 m the thickness of a biomembrane constitutes only 5 - 7 nm) and nanodiscreteness, as the basis of a cellular membrane is the bilayer of the lipid molecules (see. Fig. 2). This discreteness ensures the possibility of the simple transport (diffusion) throught membrane for the elementary molecules (first of all, for the moleculas of water) with the sizes not exceed the distance between lipids. Also this discreteness yields the backgrounds for different structural changes of a membrane, as ensures broad possibilities for the action on it by ultrasonic and other factors. If among the different possible mechanisms of action of ultrasonic on cell the acousto-mechanical factor is chosen then at the expense of the disproportion between length of an acoustic wave and sizes of a cell this factor will generate, first of all, volumetric strains of each cell and relevant strains of a membrane as cellular shell.

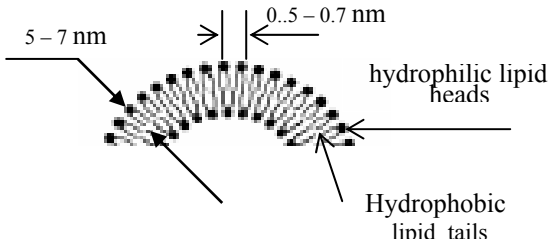

Fig. 2 Structure elements of the cellular membrane

Under any type of the strain of a membrane (the longitudinal tension - compression, flexures) will change typical distance between lipid molecules in bilayer (see Fig. 2), whose consequences can be different nanoeffects, connected with the nanodiscreteness of a cellular membrane and which essential for vital activity of a cell.

First of all, we shall yield the elementary estimate of the change of the membrane area activity of ultrasonic pressure. The precise problem of membrane area change finding under the ultrasonic action is very complicated (see, for example, [5]) and allows taking into account all spatial (spherical) harmonics giving the contribution to this change. Considering only zero harmonics corresponding to the isotropic volumetric tension /compression of a cell (for a simplicity - of the elementary spherical shape), and attracting definition and value β of the « integrated » coefficient of volume compression for a tissue consisting of cells, we have

First of all, we shall yield the elementary estimate of the change of the membrane area activity of ultrasonic pressure. The precise problem of membrane area change finding under the ultrasonic action is very complicated (see, for example, [5]) and allows taking into account all spatial

(spherical) harmonics giving the contribution to this change. Considering only zero harmonics corresponding to the isotropic volumetric tension /compression of a cell (for a simplicity - of the elementary spherical shape), and attracting definition and value β of the «integrated» coefficient of volume compression for a tissue consisting of cells, we have

$$\beta = \left[\left(\frac{R}{R_0} \right)^3 - 1 \right] \cdot \frac{1}{p_{ак}}; \qquad \frac{\Delta S}{S_0} = (p_{ак}\beta + 1)^{2/3} - 1 \approx \frac{2}{3} p_{ак}\beta \ , \qquad (1)$$

where R_0, S_0 and R, S are the initial radius and area of a spherical cell and increased they during the «negative» phase of acoustic pressure p_{ac} action. Taking for an estimate the value $\beta = 5 \cdot 10^{-5}$ atm.$^{-1}$, that corresponds to water, it is obtained from (1) that, for example, under p_{ac} = 100 MPa the relative change of the area of a cellular membrane is equal 3.3 % and corresponds of the threshold values region for its rupture [6]. Under *a fortiori* smaller acting pressures in the absence of a direct disruption of a membrane there are the requirements for the realization of the following nanoscale effects. First of all, during the change of the cellular membrane area caused by the ultrasonic action, the average distance between the lipid molecules will vary and this leads to the change of the passive transport intensity for the elementary molecules, which can penetrate through a membrane. Secondly, the initially existing the defects of the lipid packing in biomembrane structure can transform under the acoustic deformation (stretching, bending) to the so-called through pores (this is the sonoporation process) having the dynamics of its own that leads to the increasing or self-healing of the pores. Through these rather large pores by the size from several unities up to hundreds nanometers it is possible purposefully to incorporate inside of a cell the drug and/or gene material for the required correction of the own genes of the cell. This process must beginning with «the address delivery » to the cell of the necessary preparations where also noticeable role is played «the acoustical escort» of the special molecular microcontainers with these preparations. The exploitable in ultrasound diagnostics the contrast agents representative the artificial hollow lipid microspheres can be used as such microcontainers. Also induced by ultrasonic action the thermal processes and so called the secondary factors (for example, cavitation) will lead to the physiological changes in cells. All indicated processes (in basic, of the nanolevel scales) caused by the ultrasonic action on the separate cells, lead to the correction of the cellular function and then lead to the solving of the medical (therapeutic) problems in the frameworks of the already accepted «nanomedicine». The essential role of ultrasonic actions in the indicated technologies determines the «**ultrasonic nanomedicine**» as separate scientific field.

REFERENCES

1. Ginzburg V. L., About Science, Myself and Others, Taylor & Francis, 2004
2. Drexler K. Eric, Engines of Creation. The Coming Era of Nanotechnology, Anchor Books, 1986.
3. Freitas R. A. (Jr.), Nanomedicine, Volume I: Basic Capabilities, Landes Bioscience, Georgetown, TX, 1999.
4. Hesjedal T. Nanoacoustics: probing acoustic waves on the nanoscale, in Proc. of SPIE, V. 5045 (July 2003), P. 13 – 27.
5. Iljukhina M. A., Makov Yu. N., Deformation of the lipid membranes under ultrasound action and the local criterion of its destruction // Vest. Mosk. Un-ta., Ser. III “Fizika. Astronomiya”, 2005, № 5, P. 39 – 43. (In Russian)
6. Evans E. A., Skalak R., Mechanics and Thermodynamics of Biomembranes, CRC Press, Inc., Roca Ration, Florida.