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Nonlinear waves: some biomedical applications

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Contents

Abstract. **The field of nonlinear physics, item No. 11 on Ginzburg's list of "the most important and interesting problems", is reviewed. An example at the intersection of applied physics, medicine, and instrument engineering is discussed to illustrate the range and scope of the field and how deep the ideas and approaches it involves are incorporated in modern natural science and engineering. Results of relevant research and development, which has attracted much recent interest and financial support, are briefly examined.**

1. Introduction

In the article "What problems of physics and astrophysics seem now to be especially important and interesting in the early 21st century" [1], Vitalii Ginzburg presented a revised list of "most important and interesting problems" of 2001. The field of nonlinear physics is mentioned under item No. 11 of this list.

This is how Professor Ginzburg comments on his choice: "As regards nonlinear physics... There is a wealth of material, it is published in each issue of *Physical Review Letters* having a special section partly devoted to nonlinear dynamics. Moreover, other sections of the journal are also concerned with nonlinear physics; a total of 10 – 20% of all publications deals with nonlinear physics. It should be emphasized that increasingly more attention is being given to nonlinear physics. Hence, there is a variety of educational and monographic literature. It is largely the use of modern computer techniques that has allowed for the analysis of problems formerly unamenable to interpretation."

It is interesting to note that Ginzburg's first lists (see, for instance, Ref. [2]) contained no separate 'nonlinear physics' item. Instead, they included "nonlinear phenomena in a vacuum in superstrong electromagnetic fields". The author wrote: "Selection of 'most important problems' is certainly a matter of personal opinion; different views are possible and needed". Indeed, nonlinear problems in certain areas of physics, e.g., optics and acoustics, are traditionally considered especially interesting; their separate branches, such as nonlinear optics [3] and nonlinear acoustics [4], have for many years existed as self-contained scientific disciplines. In hydrodynamics, on the other hand, largely nonlinear problems have been solved for over the past hundred years without focusing attention on this fact; the word combination 'nonlinear hydrodynamics' is thus far rarely used in the literature. Another example is the Ginzburg – Landau equation being nonlinear in function Ψ, although the authors never used the word 'nonlinearity' in their original paper "On the theory of superconductivity" [5].

This means that all of physics is, on the one hand, nonlinear and nonlinear problems occur in all its fields; on the other hand, nonlinear physics may be regarded as a separate discipline. In other words, both standpoints are equally entitled to exist.

The term 'nonlinear' is appropriate to underscore when

(1) a mathematical model of a physical phenomenon is constructed based on nonlinear equations, and the solution of these equations is interesting by itself. In this case, a mathematical sense is emphasized;

(2) new phenomena stemming from the breach of the principle of linear superposition of solutions or from the interaction between physical objects are analyzed. In this case, the physical sense is emphasized;

(3) ideas, methods, or images formed in one area of 'nonlinear physics' are extended to another; then, the methodological sense is of importance and analogies can be used. Not infrequently, this sense is put into the words 'the physics of nonlinear oscillations and waves', and 'nonlinear dynamics';

(4) physicists and mathematicians working in different fields cooperate to develop a common language and terminology. This gives 'informational' sense to the word 'nonlinearity' defining affiliation with the part of the scientific community dealing with this topical and very 'fashionable' problem.

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The number of nonlinear problems in various fields of physics is becoming increasingly greater as noticed in Ginzburg's previously cited observation. In the course of time, the numbers of 'linear' and 'nonlinear' publications will be roughly comparable; then, the nonlinearity of a problem will cease to be a sufficient criterion of its topicality, and the frequency of the use of the term 'nonlinear' can be expected to decrease.

2. About nonlinear waves

Evidently, achievements in nonlinear physics are impossible to outline in one paper or report. A concrete example is to be chosen. If nonlinear physics is a newly planted tree (Fig. 1), the area of 'nonlinear waves' should be depicted as one of its main branches.

However, nonlinear waves altogether also make up a broad research avenue as fairly well illustrated by the series of books containing review lectures delivered at the 13 sessions of the School of Nonlinear Waves held in Nizhny Novgorod from 1972 to 2006 [6]. A smaller branch of nonlinear waves is nonlinear acoustics; one of its aspects, biomedical applications, is chosen here as an example. Such a choice is objectively grounded (see Fig. 1).

Why should it be medicine? Because health is an interesting topic for everyone. Why acoustics? Because the human body as a whole and its tissues are transparent to acoustic waves. Moreover, field characteristics are easy to control by focusing waves on a target organ, modulating a continuous signal, or altering acoustic pulse parameters. Finally, acoustic instruments are rather cheap and safe.

The joint general meeting of the Russian Academy of Sciences and the Russian Academy of Medical Sciences, entitled 'Science for Human Health' and held in 2003 outlined many promising applications of physics to medicine. However, acoustic studies were not the focus of the discussion, in line with the situation in Russia but in contrast to the prevailing world trend.

Some 6 – 8 years ago, acoustic diagnostic techniques won second place on the world market in terms of sales volume (25%), lagging behind X-ray units (32%) but outstripping magnetic resonance tomographs (16%). It can be predicted that acoustic and magnetic resonance devices will be in increasingly greater demand than X-ray facilities due to their safety for patients and medical personnel. Moreover, the low cost of acoustic instruments will inevitably further advance their market position.

Funding of the development of medical acoustic instruments and technologies may be estimated only by order of magnitude. In 2006, the overall budget of the US National Institute of Health amounted to 28.6 billion dollars. According to expert estimates, one half of the total covered the costs of development of new pharmaceutical products, and the other half covered developing and building new equipment and technologies. As much as 10 – 20% of this half, likely one to two billion dollars, was spent on acoustic developments. Moreover, large funds were provided by the US Department of Defense, private investors, and charities. And this picture only characterizes the situation in the United States alone.

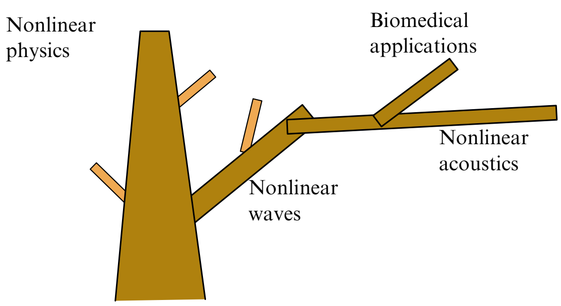


Figure 1. Location of problems under discussion amongst related branches of nonlinear physics.

Applied studies in nonlinear wave physics are arbitrarily categorized into 'informational' (the use of nonlinear waves for signal processing and transmission, medium diagnostics) and 'action-related' (transport of high energy densities, treatment of materials, initiation of various processes and reactions).

Nonlinearity imports essentially new possibilities into both categories. For example, the use of weak waves to obtain information about a medium implies variation of such their characteristics as the direction of propagation, frequency, and polarization. When nonlinearity is brought into use, a new dimension appears in the space of varied parameters. Conditionally speaking, it may be the amplitude, the intensity, or other characteristics describing the wave 'strength'. A variety of nonlinear diagnostic methods have been proposed [7]. Some of them are a simple generalization of linear approaches. For example, resonant response is possible to achieve not only at the fundamental frequency but also at harmonic and combination frequencies. At the same time, totally new possibilities appear that are lacking in the linear regime.

The two above lines of development find application in the works on biomedical acoustics. Obviously, in the 'action-related' paradigm practically all devices (used in therapy and surgery) operate in the nonlinear regime. Less evident is the fact that nonlinear waves are extensively used for diagnostic purposes.

An important advantage of acoustic instruments is their universal nature. In many cases, a single device can be used for both diagnosis and treatment. By way of example, the same ultrasonic instrument makes it possible, in principle, to detect a neoplasm, characterize (i.e., quantitatively differentiate) it, assess the degree of malignancy, and destroy the tumor. Moreover, the process of degradation is visualized (image-guided therapy).

Another instrument allows the physician to detect internal bleeding (e.g., inflicted by a highway accident), locate it, and 'seal' the injured vessel by means of remote heating by focused high-power ultrasound beam (acoustic hemostasis).

Biomedical applications of nonlinear phenomena are considered in numerous reviews both in domestic [8 – 11] and foreign [12 – 17] editions. Over 1,000 papers have been published on this theme. Almost 100 reports were presented at 12 sessions of the last Congress of Acoustic Societies of the USA and Japan (Honolulu, December 2006) [18]. It is therefore difficult now to draw up a comprehensive overview of publications concerning nonlinear biomedical acoustics; only the main areas of its further development can be distinguished.

3. On nonlinear diagnostics

Acoustic methods are widely employed in medical diagnostics. One example is ultrasound visualization of internal structures in the organism (sonography), frequently referred to as diagnostic ultrasound imaging. This technique allows one not only to tell the gender of a fetus but also to obtain a fairly legible image of its face. Modern instruments can operate in the Doppler regime, for example, for visualization of heart valve movements, and at higher harmonics for the improvement of image quality; they also afford a number of other functions. Detailed information and illustrations are available on the website of the Radiological Society of North America (www.radiologyinfo.org).

Certain methods of medical diagnostics using nonlinear properties of media and high-amplitude acoustic waves were discussed in Ref. [7]. They include visualization with the help of contrast agents in the form of stable gas bubbles in saline that are injected into a blood vessel and scatter ultrasound both linearly and nonlinearly, thus showing blood flow patterns [19, 20]. At a low bulk concentration of gas bubbles in water, $\sim 10^{-4}$, the nonlinear parameter of suspension amounts to $\sim 5 \times 10^3$ [7] compared with 3.5 and 1.2 for pure water and air, respectively. Marked local nonlinearity and a low noise level from linear scatterers at higher harmonics of the probing signal permit tracing movements of a small group of bubbles and even a single bubble, hence the possibility of visualizing the blood flow structure in selected vessels or their network in a given part of the body. Contrast agents are also used to study the contraction dynamics of the heart muscle, to locate an internal hemorrhage, and for a variety of other purposes. Bubbles normally have a radius of $1-10$ μm and are enclosed by a $4-10$ nm thick protein, lipid, or other membrane that slows down gas dissolution. Resonance frequencies usually fall in the range from several unities to a few dozen megahertz. The membrane has a pronounced effect on bubble oscillation dynamics, increasing the resonance frequency by $40-50\%$ and introducing marked viscous damping.

However, stable microbubbles are too large and can penetrate only vessels; therefore, they are largely used to visualize the blood flows. Recently proposed mechanisms allow microbubbles to be generated inside tumors, microthrombi (clots), and even a single cell. These methods can be referred to as acoustic nanotechnologies. An emulsion of nanoparticles injected into a patient accumulates in the internal organ to be examined and treated, where it gives rise to cavitation bubbles under the effect of a high-power acoustic pulse. Also used to the same purpose are nanodroplets of fluids having a boiling temperature slightly lower than body temperature; after injection, they reside in the overheated (subcritical) state. Ultrasound causes the overheated liquid to boil explosively, thus producing bubbles.

Images of internal organs, obtained from scattering the second-harmonic signal of an incident wave (second harmonic imaging), are widely used in medical diagnostics. An example is presented in Fig. 2. Clearly, the image at the second harmonic is more distinct than at the fundamental frequency. It is not only because the resolution is higher for shorter wavelengths. For intense waves, the dependence of the response on the incident wave amplitude displays a nonlinear character. Radiation focused on an internal organ undergoes amplification by $K \gg 1$ times. The response at the second harmonic gains by roughly K^2 times. Therefore, the contribution from the focal region predominates in the scattered field. When contrast agents are used, the dominant contribution is from that part of the tissue that accumulates bubbles. This mode of visualization is employed for the diagnosis of hepatic disorders (hepatocellular carcinoma, metastases) or the detection of cardiac thrombi or mucus in the gallbladder at an earlier stage of cholelithiasis, i.e., in cases of poor acoustic contrast between an object under examination and the surrounding tissues. Also, this method finds application in ophthalmology (e.g., to diagnose retinal lesions) where high frequencies (on the order of 50 MHz) need to be used; they are obtained by generating higher harmonics. Visualization at the third and fourth harmonic frequencies (super-harmonic imaging) has similar advantages.

Certain techniques are based on specialized processing of nonlinearly distorted signals. A most popular one uses inverted pulses (pulse inversion imaging). The probing signals are two quasi-monochromatic pulses containing several oscillations. The second pulse is an inverted copy of the first: signs of quasiperiods with positive and negative polarities are replaced with the opposite ones. The recorded responses of both pulses are summed up. Evidently, the total signal is zero for linear reflection. For a nonlinear reflector,

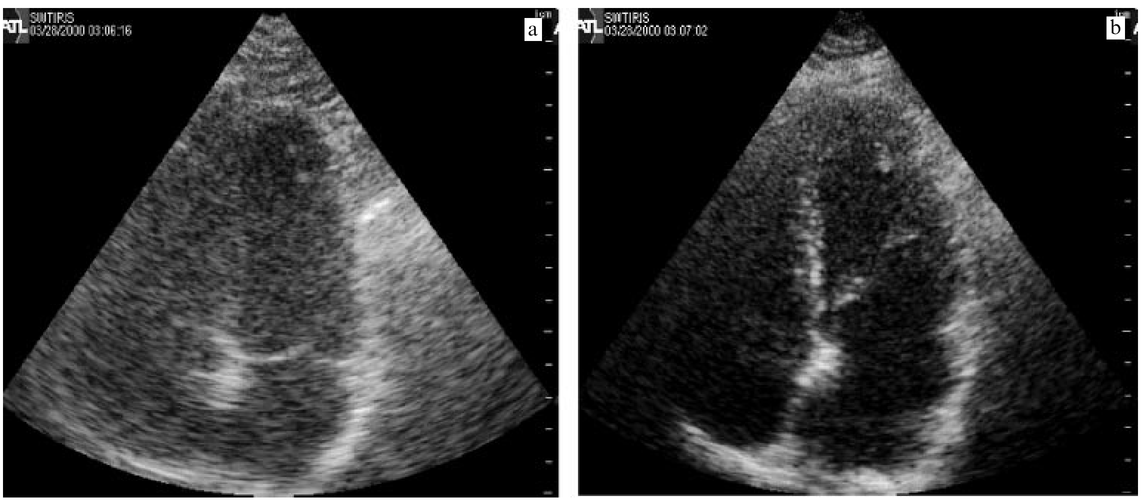


Figure 2. Acoustic image of the heart at the fundamental frequency of the probing signal (a) and nonlinear second harmonic imaging (b). Courtesy of V A Khokhlova (with permission of Dr. M A Averkiou, Philips Ultrasound, USA).

signal summation at higher even harmonics results in a doubling of its strength. Also used are sequences of inverted pulses in combination with Doppler filters to exclude noise produced by tissue motion.

The 'power-modulation' technique uses a series of pulses with various amplitudes differing, for example, twofold. The recorded echo-signals are smoothed in terms of amplitude and subtracted. The signal at the fundamental frequency is then suppressed and the response becomes purely nonlinear. A few other (essentially similar) modes of nonlinear signal processing have been proposed.

Nonlinear acoustic tomography [21] and diagnostic techniques based on remote wave excitation by pulsed radiation pressure [22] deserve special attention.

An important informative characteristic of soft tissues is their shear elasticity. Tissues are known to contain almost 80% water. Proteins and other organic and low-molecular components are virtually the same substances; their concentration is poorly differentiated. Therefore, the compression modulus and the speed of sound determined by intermolecular interaction forces are similar for all tissues to within $\sim 10\%$. Impedance and the acoustic nonlinearity parameter vary in an equally narrow range. In contrast, structural features (geometric parameters of cells, inhomogeneity, and anisotropy) undergo variation in a significantly broader range. Therefore, the shear modulus and Young modulus vary within three or four orders of magnitude. Variations amount to several thousand percent even for the same tissue, e.g., in a growing tumor or a contracting muscle [23]. Neoplasms and muscular pathologies can be diagnosed by measuring these parameters [24], as exemplified by sarcopenia (age-related muscle cell apoptosis). Sarcopenia, similar to osteoporosis, is a risk factor in bone fractures in the elderly. Acoustic methods provide a promising diagnostic tool for pathologic conditions associated with muscular atrophy and dystrophy in patients with neurologic complications and myopathia, in immobilized and bed-ridden cases, in gerontology, and in sport and space medicine [25].

The measurement of shear elasticity under radiation pressure of focused ultrasound is known as shear wave elasticity imaging (SWEI) [22]. Figure 3 portrays a shear stress zone that appears in the focal region and undergoes oscillations with the modulation frequency along the beam axis. These oscillations excite a shear wave traveling outward from the axis. Axial shift at a fixed point in time is presented in Fig. 3b. The structure of alternating maxima and minima is characteristic of the nearest zone in which a running wave is yet to be formed. However, it may fail to form at all due to the usually strong damping of shear waves in biological tissues. Measurement of displacement field parameters can be used to assess shear moduli and visualize tissue inhomogeneities. At ultrasound intensity in a transducer equaling 10 W cm^{-2}, at ultrasound frequencies of the order of several megahertz, or at kilohertz modulation frequencies, shear displacements in tissues are a few fractions of a micrometer.

Pulsed radiation pressure is also applied for remote excitation of various wave types in bones (through the skin and soft tissues). One such experiment is depicted schematically in Fig. 4a. Solution of the simplest problem, i.e., measurement of the velocity of sound in the bone tissue from a pulse delay, gives information about its calcium content. Processing of the broadband signal using filters (Fig. 4b) opens up the possibility of obtaining additional data for the diagnosis of bone and joint diseases (osteoporosis, arthrosis, etc.). This method is also applied to imaging the inner bone structure [26].

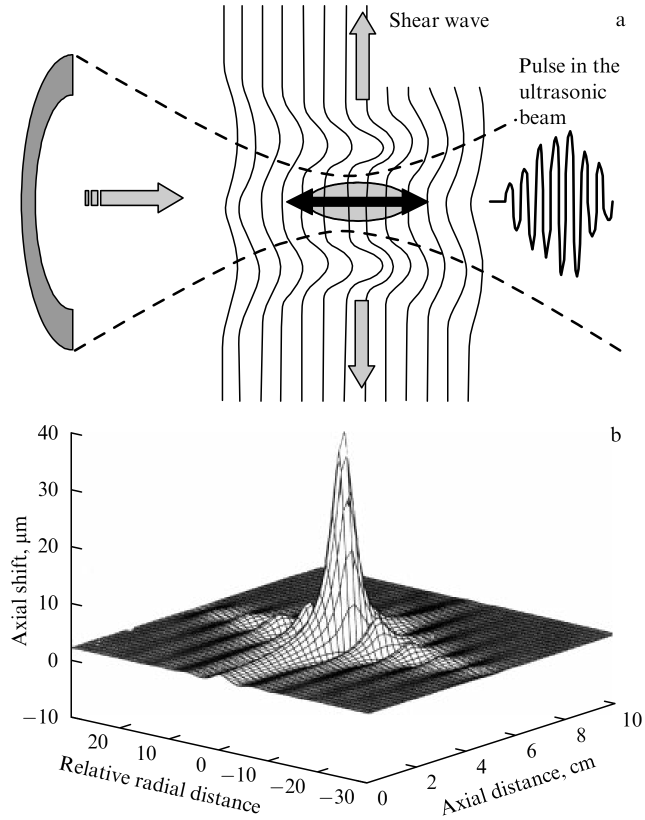


Figure 3. (a) Contactless excitation of shear waves by radiation pressure of a focused ultrasonic pulse. (b) Spatial distribution of the shear oscillation amplitude (axial shift).

M Fink proposed an efficacious method to visualize inhomogeneities of shear elasticity in biological tissues (supersonic imaging). A sequence of ultrasonic pulses is focused inside a tissue, the focusing depth of each successive pulse being larger than that of the preceding one. In this way, a 'supersonic' mobile source is formed that excites a slow shear wave (Fig. 5). In early experiments (see Ref. [27]), the 'supersonic' velocity of the source was $V \sim 6$ m s^{-1}, while the natural velocity of shear waves was $c_t \sim 2$ m s^{-1}. Parts of the propagating front bent at medium inhomogeneities exactly reproduce their contours.

Also worthy of note is the application of reversed front waves to nonlinear diagnostics [28]. These waves are used both to form a probing beam precisely focused on an object in an inhomogeneous medium due to the introduction of predistortions in the wave front structure and to improve image quality at higher harmonics.

These problems are also successfully solved by means of the 'time-reversal' methods [29]. One of the schemes here is the following. A 'point' source emits a short pulse directed toward a reverberation chamber (for instance, a pipe section with highly reflecting walls). The multiply reflected time-extended signal is recorded by broadband receivers inside the chamber. Then, the signal is amplified and emitted in the opposite direction. After multiple re-reflections in the reverse order, the signal undergoes compression (focusing in time) and transfers high energy densities to the primary point source without apparent nonlinear distortions [30]. At first

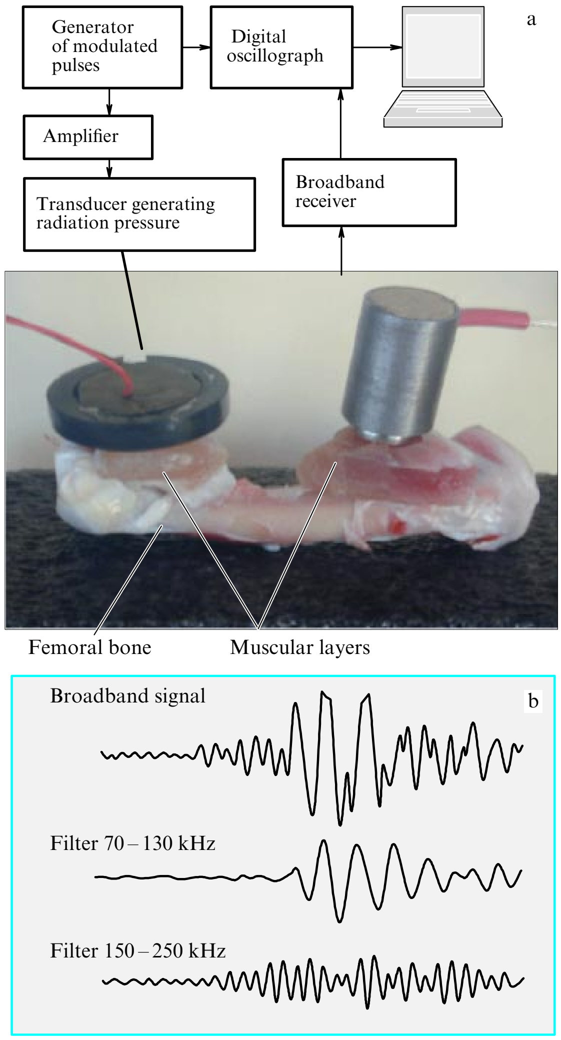


Figure 4. Schematic of wave excitation in a bone by radiation pressure (a), and the shape of the received signal (b). (Photograph courtesy of A P Sarvazyan.)

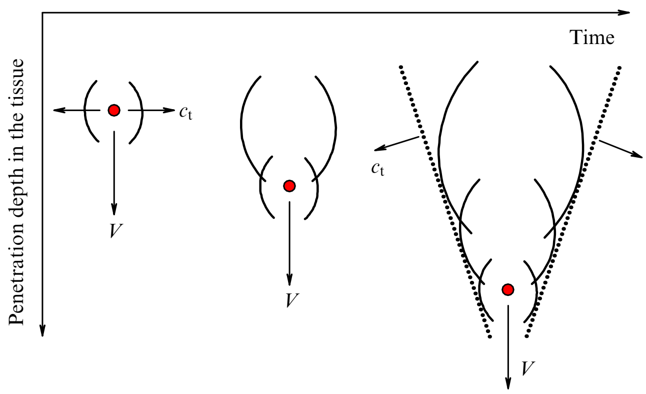


Figure 5. Excitation of a shear wave front (dotted lines) in a tissue by the moving focus of an intense ultrasound wave; a Mach cone forms when the focus propagation velocity V exceeds the shear wave velocity c_t.

sight, the method resembles pulse compression in optics, but it does not use sound velocity dispersion to compress the pulses. The knowledge of the near field structure allows the diffraction limit to be exceeded and an inverted pulse to be focused on a region much smaller than the wavelength [31]. A typical problem to be solved with this technique is focusing ultrasound on a given brain area through the cranial bones [32].

4. Nonlinear phenomena and therapy

Mechanisms of the therapeutic action of ultrasound on biological tissues are reviewed in the recent publication [11]. For this reason, certain issues considered therein at great length will be only briefly mentioned in this report. The list below enumerates the main applications of nonlinear ultrasound in therapy and surgery.

(1) Intense pulses with a shock front are used for

— extracorporeal lithotripsy (fragmentation of renal calculi and other bioconcrements with the aid of a source outside the patient's body);

— shock-wave therapy (treatment of bone diseases and articular inflammation).

(2) High-power focused ultrasound is used for

— noninvasive surgery of brain tumors;

— noninvasive ultrasound removal of benign tumors of splanchnic organs (prostate and mammary glands, liver, kidneys, joints);

— arrest of internal bleeding (acoustic hemostasis);

— cardio- and angiosurgery (arrhythmias, heart failures, thrombosis);

— ultrasound correction of body contours (noninvasive liposuction);

— accurate drug delivery to a target organ, including the use of contrast agents.

Focusing devices are used in many ultrasonic therapeutic facilities to amplify the effect of ultrasound on biological tissues. The role of nonlinear factors increases considerably during the concentration of energy. Moreover, the complicated frequency-dependent dissipative properties of biological tissues need to be taken into consideration; equally important is diffraction in the focal region. The effects of these factors on the field amplification coefficient at the focal point are discussed in the review [33, sections 5, 6]. It should be recalled that the formation of shock fronts in the profile of intense acoustic waves is followed by their sharply accelerated damping. In modern focusing devices for medical application, field intensity at the focal point amounts to several kilowatts per cm^2, with nonlinear wave absorption being one order of magnitude higher than the linear one. In many situations, saturation occurs, i.e., wave intensity at a distance from the source cannot exceed a certain limit despite an increase in its initial value [34].

Figure 6a shows changes in radiation force F and total power W along the axis of a beam focused on an absorbing biological tissue [9]. The temperature increment due to ultrasound absorption behaves similarly to F. The effect of nonlinearity (solid curves) is described by the ratio of focal distance d to shock formation length x_{sh}, which equals 0.5. It can be seen that the power first decreases smoothly with distance due to linear dissipative loss; nonlinear damping accounts for a dip near the focus. Intensity in the focus reaches a maximum; it decreases at the shock front due to nonlinear losses. In contrast, radiation force and temperature peaks increase with increasing nonlinearity, while their widths characterizing the locality of action decrease.

When shock fronts form between the radiator and the focus, nonlinear losses are responsible for a decreased linear value (for weak waves) of the amplification coefficient K. In

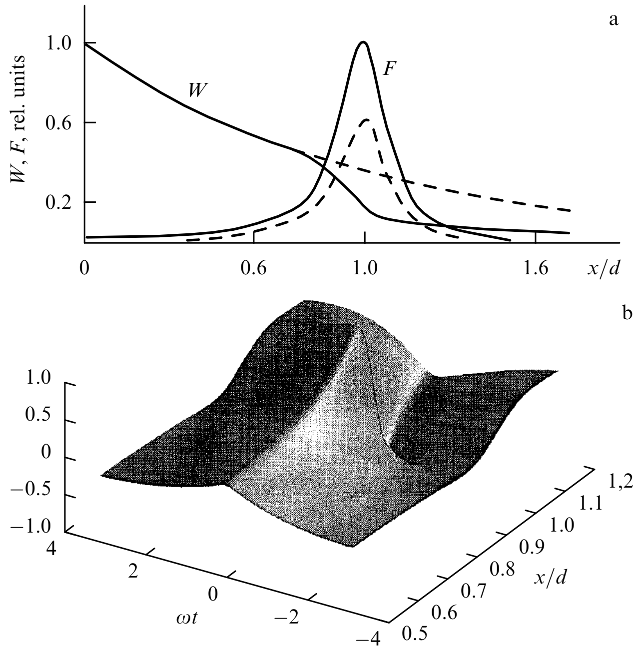


Figure 6. (a) Distance-dependent changes in a focused beam power W and radiation force F; dashed curves correspond to a linear dissipative medium, solid curves are drawn with regard for nonlinearity (the ratio of focal distance d to shock formation length x_{sh} is 0.5). (b) Example of the solution of a nonlinear inverse problem of profile synthesis of a broadband periodic wave converted into a discontinuous sawtooth-shaped wave under the combined effect of nonlinearity, diffraction, and dissipation near the focus.

the presence of diffraction, however, nonlinearity cannot only decrease but also increase K by virtue of 'sharper' focusing of higher harmonics generated by the fundamental-frequency wave [35]. Such a situation occurs when nonlinear damping on the way to the focal point does not lead to substantial energy losses; in other words, a sawtooth-shaped wave, if any, is formed just in front of the focus. This means that the parameters of a nonlinear focusing system need to be optimized in order to have large K.

Many applications depend on high locality of ultrasound action. Hence the necessity of bringing out as large radiation forces and temperature increments as possible or steep shock fronts in a small medium volume. However, diffractional phase shifts between harmonics may broaden the shock front, thus decreasing the radiation force (temperature) maximum and widening the region of its localization. Such an undesirable effect can be compensated for by generating on the transducer a complex-shaped profile with a given amplitude-to-phase ratio between constituents of its frequency spectrum. The ratio is chosen in such a way that the combined effects of nonlinearity, diffraction, and dissipation lead to shock front formation in close proximity to the focus. Then, high-density energy transport is feasible (without substantial losses on the way from the transducer to the focal point), providing a local release of energy in the focal region (by 'switching on' nonlinear absorption).

A nonlinear inverse problem needs to be solved in order to synthesize a profile of special shape [9]. A relevant example is presented in Fig. 6b. It can be seen that a nonharmonic smooth profile (only one period is shown) transforms during propagation and becomes discontinuous as it approaches the focus.

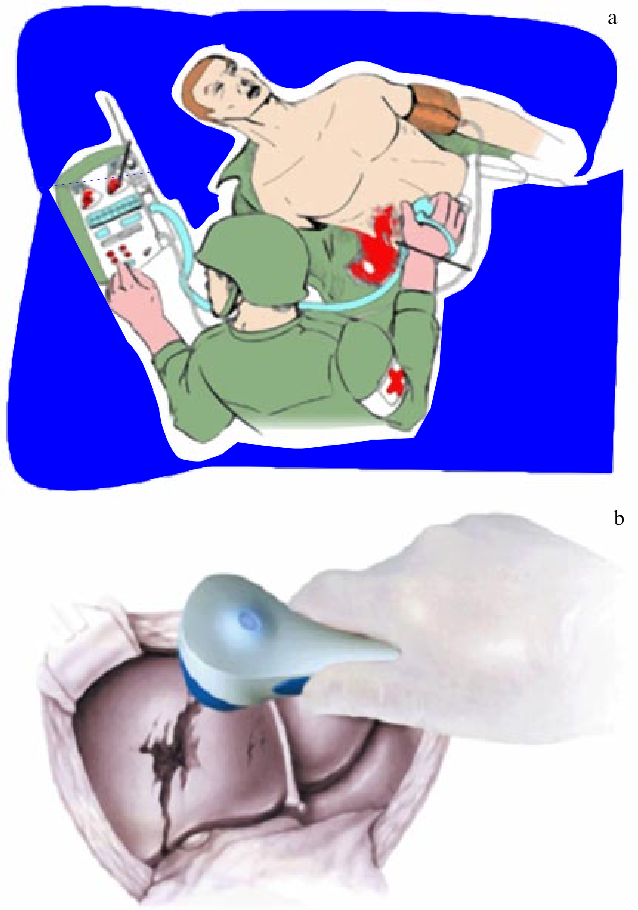


Figure 7. Ultrasonic hemostasis in an injured internal organ (with permission of Prof. L Crum, Applied Physics Laboratory, University of Washington, lac@apl.washington.edu).

Modern focusing systems ensure rapid (for several seconds) heating of the tissue in the focal region (by dozens of degrees), so that no time is left for its natural cooling due to enhanced blood circulation (perfusion). High temperature causes denaturation of protein molecules, vascular occlusion, and tissue decomposition (including malignant neoplasm). Structural changes in the treated tissues combined with enhanced 'rigidity' reinforce their scattering properties and increase shear elasticity. These phenomena are used to monitor the temperature field during irradiation. Remote temperature measurements are equally feasible in intact tissues by acoustothermotomography [36] (from thermal acoustic irradiation at megahertz frequencies, combined with probing the heated region [37]).

Figure 7 illustrates the principle of arrest of an internal hemorrhage, making use of the thermal action of intense ultrasound [38]. Internal bleeding results from injuries inflicted by catastrophes, acts of terrorism, or military actions and accounts for a 40% mortality rate among the casualties. On-site medical aid is of primary importance when urgent hospitalization is impossible. An injured internal organ is visualized by ultrasound scanning; thereafter, high-power ultrasonic radiation is used to locally heat the broken vessel and 'seal' it.

A similar combination of ultrasound diagnostic and therapeutic modalities using a single device is practiced for hyperthermia (tumor cell destruction by overheating) or ablation (tumor removal by cauterization). In such cases,

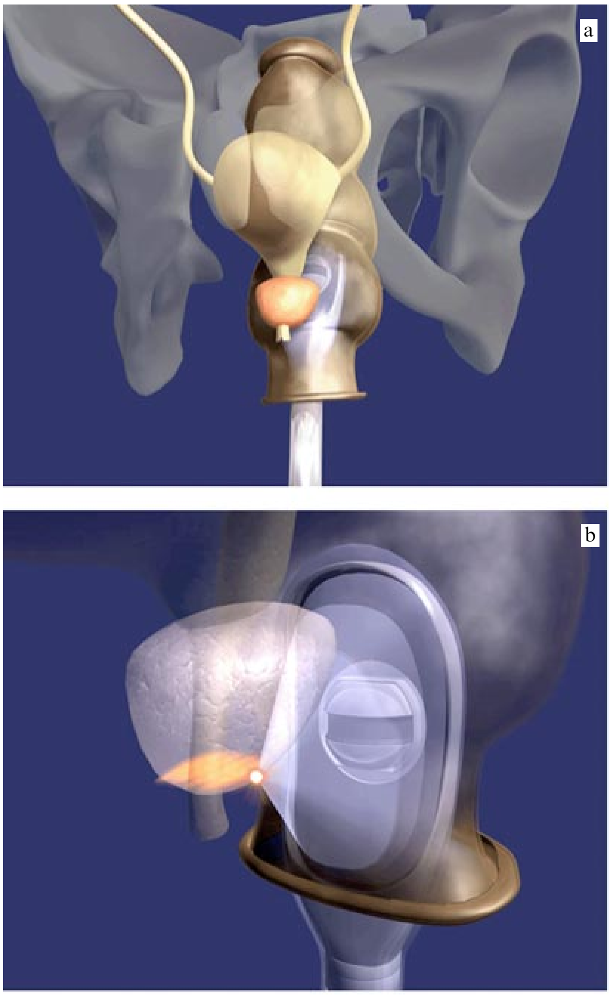


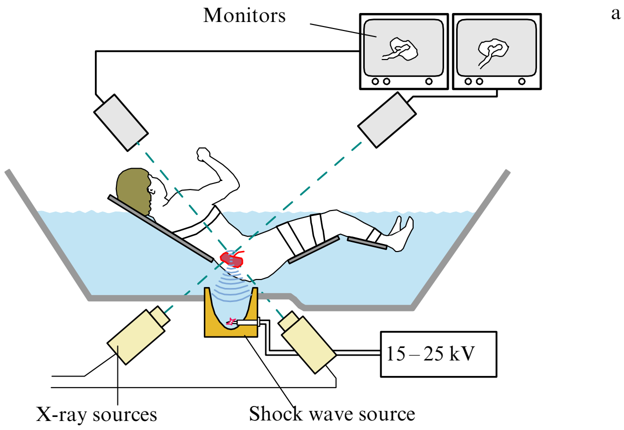
Figure 8. Thermal action of ultrasound on the prostate gland (courtesy of Dr. J-Y Chapelon, INSERM, France, with permission of EDAP, France).

the source of ultrasound is brought as close as possible to the target organ in order to minimize injurious effect on healthy tissues. An example is transrectal prostate ultrasonography (Fig. 8).

Lithotripters designed in the early 1980s are currently widely used in clinical settings (Fig. 9). They appear to be the first commercial medical devices operated in the nonlinear regime. The history of extracorporeal lithotripsy is reviewed in Refs [8, 11]. Concrements are disintegrated by a sequence of pulses (around 10^3) of microsecond duration having a shock forefront. Peak positive pressure at the front amounts to 10^7-10^8 Pa; negative pressure in the rarified zone behind the front is an order of magnitude smaller. Investigations into the mechanisms of disruption and safe efficacious treatment techniques are reported in Ref. [11].

The following fracture mechanisms can be distinguished: spallation of the rear part of the calculus due to the high negative stress at its back surface, generated under pulse reflection; formation of destroying shear stress during pulse interaction with boundaries and inhomogeneities; fatigue damage resulting from multiple reloading/unloading processes, and cavitation erosion.

The last of these is illustrated by Fig. 10. Negative pressure in an acoustic pulse triggers the creation and growth of gas bubbles from the nuclei present in the fluid and at the calculus surface. Positive pressure causes collapse of these bubbles.



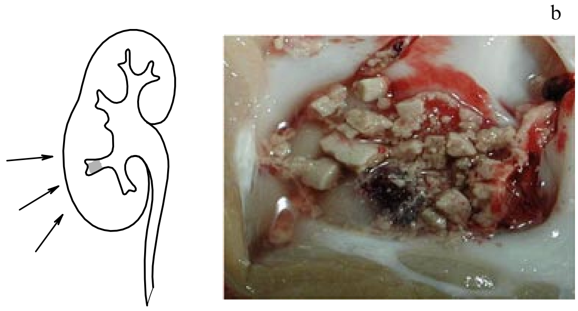


Figure 9. (a) Extracorporeal lithotripter (courtesy of O A Sapozhnikov). (b) Schematic representation of calculus location in a kidney and calculus image after fragmentation (with permission of Prof. A McAteer, Indiana University).

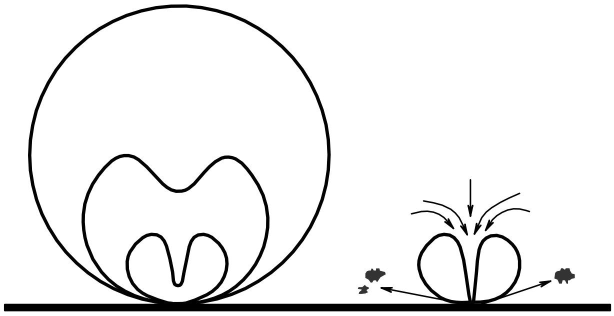


Figure 10. Instability of the spherical collapse of a single cavitation bubble near the solid boundary: the asymmetric collapse produces a high-speed cumulative jet causing erosion.

Collapse of a single bubble near the solid boundary results in the break of spherical symmetry and the formation of a cumulative jet that collides with the surface at a high speed and thereby produces a local injury. Collapse of a bubble cloud (cavitation cluster [11]) leads to similar erosion. These mechanisms not infrequently act together. For example, large calculi are first split into smaller fragments that are further disrupted due to cavitation erosion.

Injections of a gas bubble suspension or emulsion of nanoparticles are used not only to obtain acoustic images (see Section 3) but also to deliver drugs to a target organ. Biological barriers (vascular walls, intratissue space, cell membranes) are known to reduce therapeutic efficiency of pharmaceuticals. An intravenously injected drug is spread by circulation throughout the entire body, and only its small fraction diffuses across vascular walls, reaches the diseased organ, and penetrates into it through the membranes. In particular, a systemic toxic effect of potent chemotherapeutic agents may be unacceptably high or mask its curative action.

The targeted drug delivery (TDD) method is based on injection of stable gas bubbles or liquid nanoparticles to which microquantities of a drug are bound. These complexes accumulate in a lesioned organ, e.g., they may be retained in the porous structure of a rapidly growing tumor. The accumulation is possible to visualize by the acoustic imaging technique. Moreover, ultrasound may be applied to accelerate drug delivery to a target organ by means of produced radiation pressure. After accumulation of a drug in a neoplasm or a blood clot, intense ultrasound initiates the formation of larger cavitation bubbles (microbubbles or nanodroplets serving then as cavitation nuclei). Thereafter, the large bubbles collapse giving rise to jets, as shown in Fig. 10. High-speed microjets act like a syringe needle; they make holes in cellular membranes and bring in drugs and even genes. In addition, drug delivery is accelerated either by an ultrasound 'burst' of overheated nanodroplets or by decomposition of the outer coating of the encapsulated drug with ultrasound in the proximity of the target.

The majority of the works reviewed in this paper have been done in foreign laboratories. However, Russian scientists also have obtained a number of remarkable results. Studies carried out at the Laboratory of Anisotropic Structures (LAS), Russian Academy of Sciences, deserve special note. The laboratory was established by a decision of the country's leadership and worked from 1950 till 1957 under the guidance of A K Burov, an outstanding engineer and architect. Other eminent scientists were involved as well. LAS constructed quartz transducers of record-breaking power up to 12 cm in diameter that generated megahertz ultrasound fields of intensity close to 500 W cm^{-2} in an unfocused beam. The researchers observed nonlinear wave phenomena, such as harmonic generation, shock wave formation, and beam self-action. Designed for applied studies, LAS nevertheless laid the base for the development of nonlinear wave physics in this country.

In one of the LAS studies, animals were inoculated with a highly malignant Brown – Pearce tumor. Short-term irradiation (in the absence of thermal action) was applied on days 8 – 11 after inoculation when the tumor was as large as 40 cm^3. It resolved within a few months in 40 – 80% of the animals. Interestingly, metastases also disappeared even though they were not purposefully affected by ultrasound. These reassuring results gave impetus to a clinical study organized by N N Blokhin at the Institute of Experimental Pathology and Therapy of Cancer (now the Oncological Research Centre). About 10 patients (largely volunteers) with terminal stage melanoma received treatment for a cure (Fig. 11). A few cases of complete recovery were documented [39].

This result may plausibly be explained in light of the present-day data available from molecular biology and nonlinear acoustics [40]. It was noticed that metastases resolved when irradiation was applied from a distance commensurable with the shock formation length, i.e., when the wave incident on the tumor had a steep shock front a few fractions of micrometer in width and 10^{-10} s in duration. The corresponding pressure gradients at the front were sufficient to destroy cells and subcellular structures. Moreover, giant accelerations at the front (on the order of 10^9 g) could disrupt these structures by forces of inertia arising from spatial inhomogeneity of density and shear elasticity. Enzymes released from disrupted tumor cells (first and foremost telomerase) 'warn' the body about the appearance of malignancy and induce an immune response. This hypothesis is confirmed by the results of successful experiments at LAS designed to develop an autovaccine. Cancer tissue was homogenized, treated with ultrasound, and centrifuged; the supernatant was injected into a sick animal. Similar effects have recently been observed in the USA and China (see Ref. [11]). Unfortunately, these studies were discontinued in this country after Burov passed away and LAS was closed.

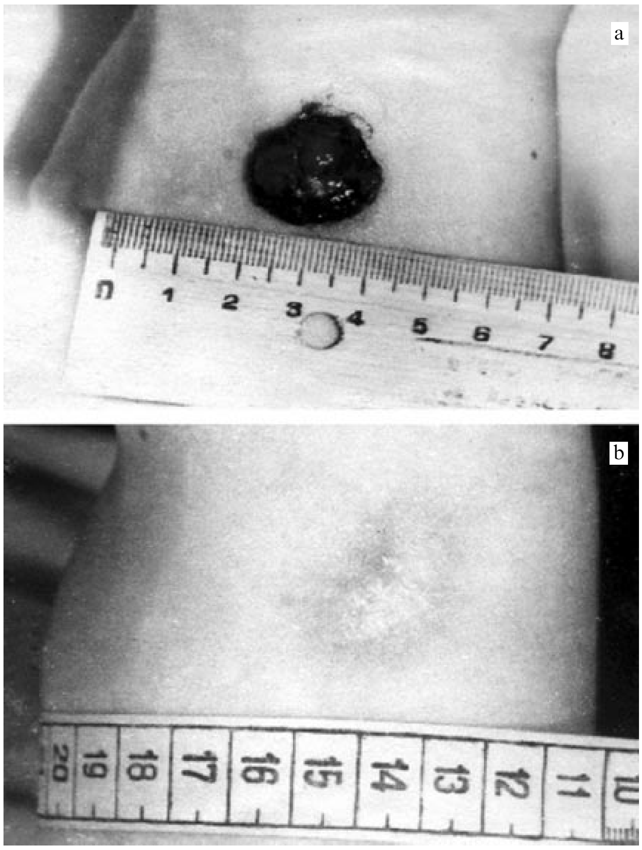


Figure 11. Primary melanoblastoma on the patient's forearm before (a) and after (b) treatment by high-intensity ultrasound (courtesy of V A Burov).

5. Conclusion

This paper was designed to discuss different views on the expediency of classifying 'nonlinear physics' as a self-contained area of research as proposed by Ginzburg in his last lists of the "most important and interesting problems". The extension of 'nonlinear approaches' to various fields of modern science and technology is illustrated by a concrete example, viz. nonlinear biomedical acoustics at the junction of applied physics, biomedicine, and the medical instrument industry. The research and developments presented in this review have recently attracted much attention and funding.

Additional information about biomedical ultrasound research in this country is contained in the monographs [4, 42]. New results have recently been obtained in the framework of expanding international cooperation [25, 43]. The most interesting data are obtained in joint studies by physicists and medical specialists. By way of example, Yu N Makov, N N Petrishchev, and co-workers recently proposed increasing myocardium resistance to ischemia by intensive ultrasound treatment [44]. The book [45] newly translated into Russian may prove interesting to physicists.

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