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Express diagnostics of DNA oligonucleotides

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The spectral characteristics of multiple Andreev reflection in a silicon nanosandwich structure are investigated. A possible mechanism of generation and recording of radiation under conditions of formation of Andreev molecules containing single carriers tunneling through dipole centers with negative correlation energy is considered. Electroluminescence spectra obtained in the analysis of different breast diseases (normal, fibroadenomatosis, terminal cancer) are analyzed. An optical version of multiple Andreev reflection, which may be of interest for the rapid identification of DNA oligonucleotides, is demonstrated.

Keywords: quantum interference, DNA identification, quantum Hall effect, oscillations Shubnikov-de Haas, quantum conductivity ladder, Faraday electromagnetic induction.

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Introduction

Terahertz radiation (THz) corresponds to the frequency range between the far infrared (IR) and ultrahigh frequency (microwave) ranges. This range has long been unattainable for research, since there are no stable natural sources on Earth that would work at room temperature, as well as the Earth's atmosphere itself does not allow radiation to pass into the region of this spectrum. The development of technology made it possible to obtain THz radiation using induced radiation from substances such as lithium niobate, semiconductors A_3B_5, which led to the creation of the technique of THz time-domain spectroscopy (THz-TDS) [1,2]. Following this, work began to appear on the study of the properties of various materials in this area of the electromagnetic spectrum. In addition, it was found that many biological objects have vibrational modes in the THz range. In the pioneering study B.Fischer and co-authors [3] obtained absorption and reflection spectra of DNA molecules in the THz spectrum. It follows from the results of this work that there is a clear frequency distinction between adenine (A), guanine (G), thymine (T) and cytosine (C), which opens up great prospects for the creation of optical techniques for the identification of DNA oligonucleotides. This fact gave a starting point for the appearance of papers on the definition of various epiginetic diseases, in particular oncological ones, since they change the structure and composition of healthy DNA, which can be seen in a change in the THz spectrum of an individual. As an example of such studies, one can cite the work of Cheon with co-authors [4], which show that one common feature is manifested in various types of cancer (lung, skin, breast, etc.) which is the presence of oncological methylation. The addition of a methyl group to cytosine, in general, occurs in small amounts in the DNA molecule, however, in the presence of an oncological disease, the amount of 5-methylcytosine sharply increases, which manifests itself in the THz spectrum of cancer cells in the form of a resonant peak at frequencies around 1.7 THz, slightly different depending on the type of cancer. Moreover, it was found that a number of basic biochemical reactions in the human body, such as ATP hydrolysis, hemoglobin oxygenation, and hydrogen bonding correspond to the energy of THz radiation, which shows a clear prospect of its use not only for the practical implementation of the optical analogue of DNA sequencing, but also for the treatment of various diseases.

Despite the seemingly huge prospects for the use of THz radiation in medicine, progress in this area is hampered by the current level of technology. The main sources of THz radiation in the current studies are three types of sources — thermal, electronic and phononic. Thermal sources, such as globars, high-pressure mercury lamps, make it possible to obtain a fairly wide range of radiation, but there is no possibility of frequency tuning in it. Electronic sources are either huge expensive installations, such as synchrotrons, gyrotrons and free electron lasers, or they have a frequency limitation of the emitted radiation of the order of 1 THz and its restructuring (traveling reverse wave lamps, resonant tunnel diodes, etc.). The most promising at the moment, both in terms of the range of available frequencies and the degree of tuning, are high-temperature superconductors (HTS), mainly of the $Bi_2Sr_2CaCu_2O_{8+\delta}$ type, however, they require cooling to temperatures of the order of 15–70 to [5]. Photonics devices, unlike solid-

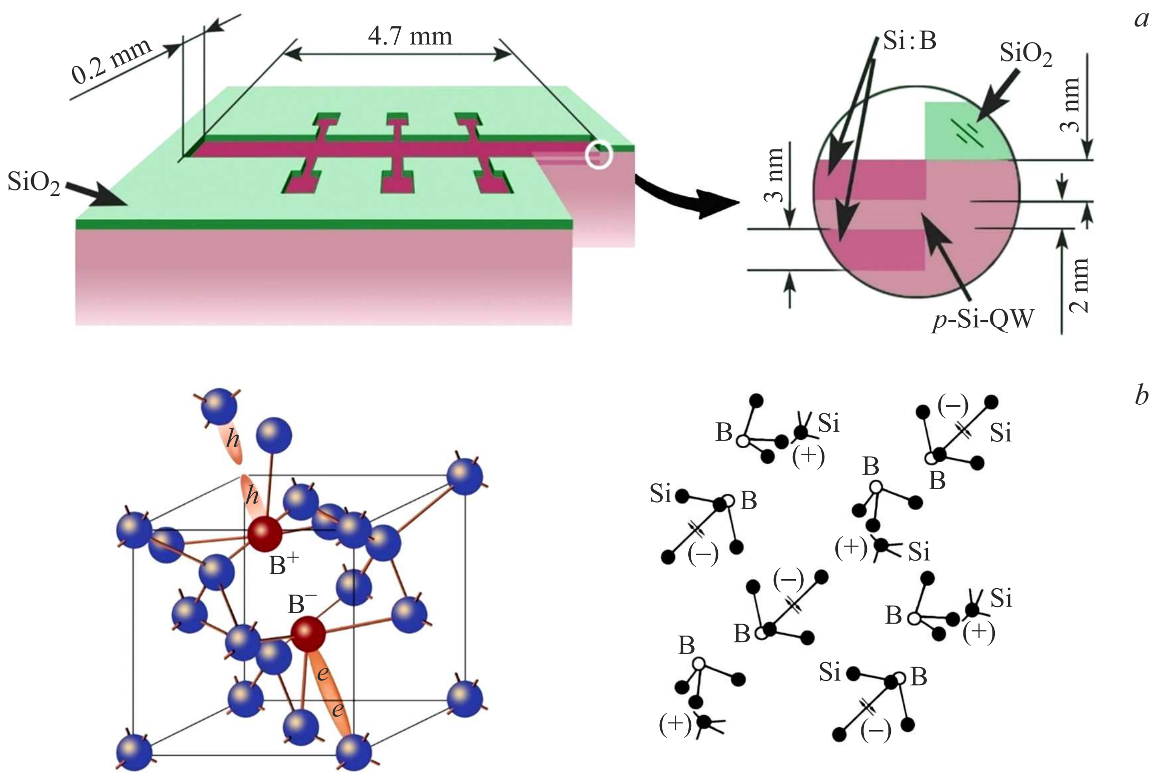

Figure 1. *a* — design of SNS with typical dimensions, *b* — dipole trigonal center of boron (B^+-B^-) with negative correlation energy and chains of boron dipole centers in δ-barriers limiting an ultra-narrow silicon quantum well.

state electronics, approach the „terahertz gap" from the high frequencies of tens of THz. Quantum cascade lasers, which are used everywhere in IR Fourier spectroscopy, require cooling to temperatures of the order of 200 K [1]. In addition, a small adjustment of the operating frequency significantly limits their use for the purposes of practical medicine. Low-noise bolometers cooled to liquid helium temperatures are most often used as THz radiation receivers. However, the development of nanotechnology in the field of semiconductors has made it possible to obtain compact solid-state devices operating at room temperature, capable of acting both as sources and receivers of THz radiation [6].

The possibilities of using a THz source based on a silicon nanosandwiches (SNS) to create an optical version of the express diagnosis of DNA oligonucleotides are considered. Previously, this THz source was tested in practical medicine in the field of traumatology, burn therapy, neurology, treatment of COVID-19 [6,7]. The proposed THz diagnosis, taking into account the mechanism of oncological methylation, can be used for early detection of breast cancer [8]. The main attention in this paper is paid to the analysis of the mechanism of THz radiation from the SNS, as well as the mechanism of reception by the same structure of THz radiation reflected from a biological object within the framework of the multiple Andreev reflection model.

1. Materials and methods

The study of structures containing Josephson contact has the greatest prospects in the field of THz radiation sources. Moreover, the main interest is concentrated on the use of topological semiconductor structures with edge channels [9,10]. Spin-dependent transport in the edge channels of such structures is enhanced due to the built-in ultra-shallow p^+-n-junction. The edge channels along the SNS perimeter are limited by δ-barriers strongly doped with boron (Fig. 1, *a*). This structure was obtained on (100) silicon substrate of *n*-type of conductivity during pre-oxidation and subsequent short-term diffusion of boron from the gas phase [6]. It was shown that boron atoms in δ-barriers form trigonal dipole centers (B^+-B^-) due to the negative-U reaction: $2B^0 \rightarrow B^+ + B^-$ (fig. 1, *b*) [11]. The transverse dimensions of δ-barriers were 2×2 nm. The studies of cyclotron resonance and spin-dependent recombination showed that carriers (holes) have a long relaxation time in the edge channel due to the suppression of the electron-electron interaction, which made it possible to observe such macroscopic quantum effects as the quantum Hall effect, Shubnikov–de Haas effects and de Haas–Van Alphen, Aharonov–Bohm oscillations [11]. These measurements allowed determining the value of the two-dimensional density of holes, which was $p_{2D} = 3 \cdot 10^{13}\,m^{-2}$. A system of consecutive „pix-

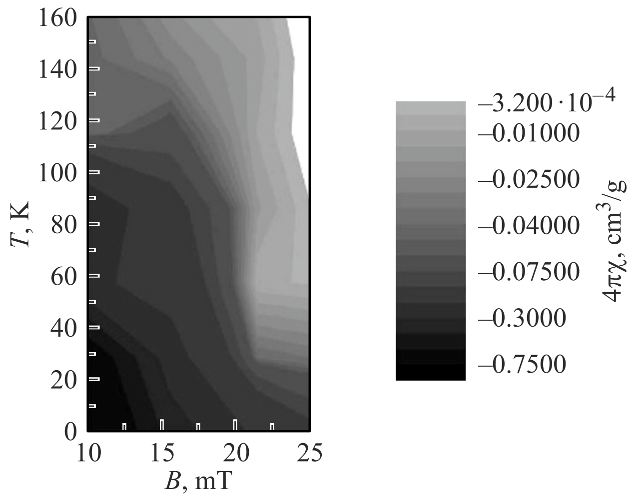

Figure 2. $T-B$ diagram demonstrating the diamagnetic response of magnetic susceptibility due to edge channels in SNS. The presence of consecutive correlation slits with different values of $2\Delta = 3.52\,kT_C$ is demonstrated: $2\Delta = 44$ meV, $T_c = 145$ K; $2\Delta = 33.4$ meV, $T_c = 110$ K; $2\Delta = 27.3$ meV, $T_c = 90$ K; $2\Delta = 22.8$ meV, $T_c = 75$ K; $2\Delta = 7.6$ meV, $T_c = 25$ K.

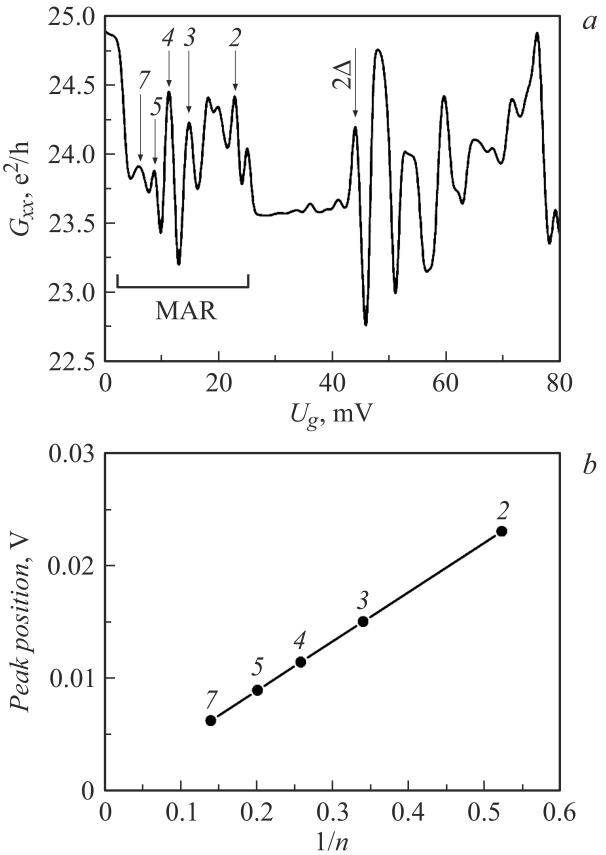

Figure 3. *a* — Current-voltage curve of Andreev reflection ($2\Delta = 44$ MeV) attributable to the presence of pixels containing single holes in the edge channels of the silicon nanosandwich structure; *b* — energy positions of the peaks of Andreev reflection depending on the peak number.

els“ ($16.6\,\mu$m$\times 2$ nm) containing single holes is formed in the edge channel (length 4.7 mm) [11]. Since the pixel is limited by boron dipole centers with negative correlation energy, in conditions of electric transport, single holes tunnel through them in the opposite direction [11].

Moreover, the change of the direction of tunneling is accompanied by a reversal of the spin of the hole. Thus, each pixel containing a single hole can be considered as an Andreev molecule, within which multiple Andreev reflection can manifest itself [12]. Moreover, the Andreev molecule, limited by chains of centers with negative correlation energy, exhibits superconducting properties due to tunneling of single carriers through dipole centers [13,14]. It should be noted that quantum-like mechanical tunneling is characterized by an increase of the critical temperature of the superconducting junction [11]. The Andreev molecule is characterized by an increase of the probability of Josephson junctions and multiple Andreev reflections to the opposite boundary at its edges. The properties of a pixel as an Andreev molecule are reflected in the results of the study of the electrical, magnetic and optical properties of the SNS. The corresponding change of spin and the movement of the hole in the opposite direction can be controlled by changing the magnetic field, the magnitude of the longitudinal current and/or voltage applied perpendicular to the edge channel, which is reflected in the presence of a diamagnetic response of static magnetic susceptibility (Fig. 2), as well as when recording multiple Andreev reflection spectra (Fig. 3). It should be noted that in the presence of several consecutive pixels relative to the edge of the SNS, several versions of multiple Andreev reflection may occur, differing in the value of the critical temperature (Fig. 2) and, accordingly, the value of the critical gap $2\Delta = 3.52\,kT_c$ (Fig. 4) [15]. In this case, a single hole tunneling in a pixel interferes with its own image on the opposite chain of negative-U dipoles, i.e. the lateral sequence of pixels relative to the edge channel can be considered as a system of Andreev molecules with different widths and, accordingly, with different values of the correlation gap. Thus, the Andreev molecule under conditions of induced longitudinal current is a source of

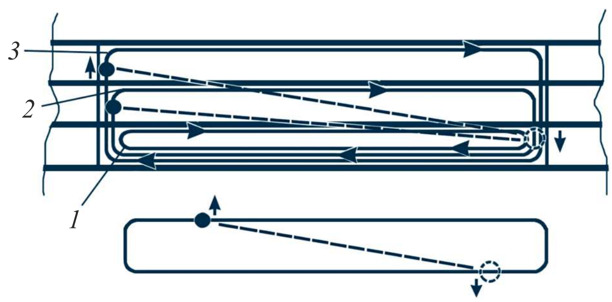

Figure 4. Quantum interference of a single hole in a pixel system with a different value 2Δ in edge channels of the SNS. 2Δ, meV: *1* — 44, *2* — 33.4, *3* — 27.3.

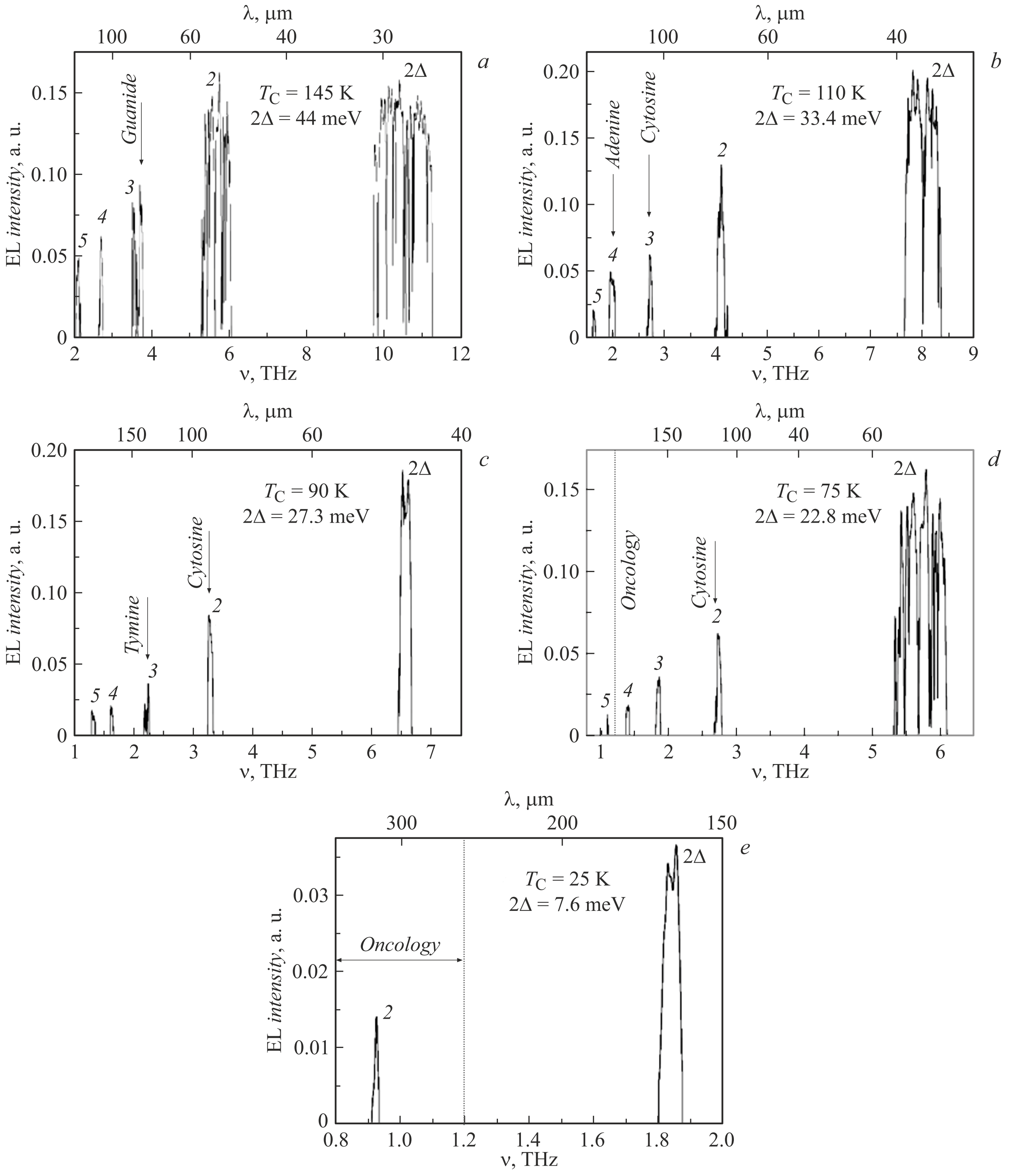

Figure 5. Spectra of electroluminescence induced by the multiple Andreev reflection of holes in pixels with different value of 2Δ. The positions of the peaks correspond to the data of electrical measurements of the spectra of multiple Andreev reflection (Fig. 3). 2Δ, meV: *a* — 44, *b* — 33.4, *c* — 27.3, *d* — 22.8, *e* — 7.6. The conformance of the electroluminescence spectra with the energy positions of the spectra of DNA oligonucleotides is shown.

long-wave radiation in the process of quantum interference of holes with the multiple Andreev reflection. It is important to note that the ballistic properties of chains of boron dipole centers with negative correlation energy allow expecting a high quantum yield in a wide spectral range under conditions of a multiple Andreev reflection, which is demonstrated by recording electroluminescence spectra by IR Fourier spectroscopy using Bruker Vertex 70 spectrometers. The electroluminescence spectra strictly conform with the positions of the peaks of the multiple Andreev reflection at the used energy values of the correlation gaps 2Δ, $h\nu = 2\Delta/n$, where n — peak number under conditions of the multiple Andreev reflection. It should be noted that the electroluminescence spectrum simultaneously reveals all versions of the multiple Andreev reflection, which are shown in Fig. 5.

Moreover, the spectra demonstrating the optical version of multiple Andreev reflection are characterized by the presence of Rabi splitting [16] due to microresonators embedded in the edge channel system, as well as GHz modulation, in particular due to the excitation of the neutral boron center.

2. Results and discussion

Sources of THz and GHz radiation based on Andreev molecules can be used for the diagnosis of oncological diseases. As noted, oncology makes a change in the composition of the DNA molecule of a healthy person, which leads to a change of the radiation spectrum and the appearance of a new peak at a frequency of about 1.7 THz, characteristic of a large number of 5-methylcytosine molecules. In addition, an increase of the radiation signal, as well as a shift of the main peaks at frequencies of 2.8−3 THz to the lower frequency region is observd (Fig. 6). This spectrum is interpreted on the basis of a combination of the mechanisms of occurrence of Faraday electromagnetic induction and multiple Andreev reflection. In this case, it is possible to estimate the generation current in a pixel that occurs under conditions of registration of radiation reflected from a biological object: $I_{gen} = \frac{dE}{d\Phi} = \frac{h\nu}{\Phi_0}$, (where dE — change in energy, $d\Phi$ — change of magnetic flux, Φ_0 — quantum of magnetic flux), i.e., it is possible to determine the frequency of the radiation reflected from the biotissue based on the magnitude of the recorded generation current. In addition, the received photons can induce junctions between the edge channels, which lead to a change of the conductivity of the system. Thus, the SNS can simultaneously be used as a source and receiver of THz radiation. The device containing the SNS during the experiment was held at a distance of about 1 cm from the skin in the immediate area of localization of pathology. All the volunteers had verified diagnoses, as well as the results of ultrasound and mammograms, which made it possible to determine the location and size of tumors. Figure 6 shows the experimental response of THz radiation from biological tissue in four breast conditions: diffuse fibroadenomatosis, nodular fibroadenomatosis, the initial form of breast cancer and breast cancer with a tumor ranging in size from 2 to 5 cm and metastases in axillary lymph nodes. It can be seen that the red spectrum is characterized by the presence of peaks in the

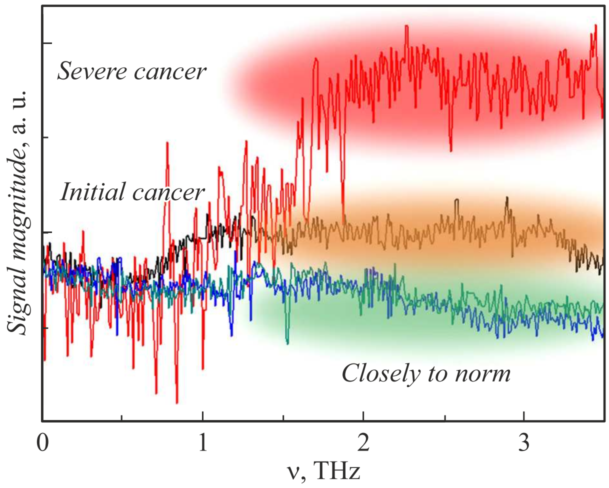

Figure 6. Terahertz response from biological tissue in fibroadenomatosis (blue and green lines), early stage cancer (black) and late stage cancer (red line).

region of 2.8 THz, corresponding to the resonant peaks of guanine (2.9 THz) and cytosine (2.7 THz). The described peak is traced in the spectrum at a frequency of 1.7 THz, characteristic of oncological disease [4]. Peaks can be distinguished at frequencies of 2.5,THz (thymine), 2.9,THz (guanine) and 3.2,THz (adenine) in the black spectrum, while thymine and guanine predominate in the blue and green spectrum.

Conclusion

It is shown that Andreev molecules in the edge channels of nanostructures can be used both as a source and receiver of THz radiation. The mechanism of emission and reception of THz radiation based on multiple Andreev reflection is presented. An example of recording of electroluminescence is given, demonstrating the THz response from biological tissue in various breast diseases (normal, fibroadenomatosis, the fourth stage of oncology). The optical version of the multiple Andreev reflection is of great interest for the express identification of DNA oligonucleotides.

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Compliance with ethical standards

All procedures performed within the human subject research were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and later amendments or comparable ethical standards.

Informed voluntary consent was obtained from each study participant.

Conflict of interest

The authors declare that they have no conflict of interest.

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