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Cancer-Specific Resonances

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Abstract

The research of cancer-specific resonances started with Raymond R. Rife's controversial results. The intensive debate began on the topic, and various interpretations of the results deepened after his death. This theme presently sparks desperate debates with extreme opinions, from the dangerous quackery to the brilliant discovery. A part of medical practices applies the resonance principle in various anticancer therapies and uses a variety of devices. Most medical experts refuse such "resonance therapies" due to their confidence in their quackery. I summarized some present problems and proposed a possible solution. My present article aims to discuss some aspects of the biological resonances, trying to clear some vague details of this subject and give a possible stochastic explanation of some resonances in cancer therapy. However, when considering the stochastic explanations of resonance frequencies, there are as many of these as there are enzymatic processes affecting the biological systems.

Keywords

Rife Frequencies, Pythagorean Mystics, Resonances, Noises, Fluctuations, Stochastic Processes, Enzymatic Resonances

1. Introduction

The resonance embraces a broadcategory of systems, especially reaction on a periodic excitation. Resonance occurs in many interactions: mechanical (e.g. strings, acoustic, tuned vibrations, etc.), electrical (e.g. tuned circuits for selectivity, impedance extremes, etc.), atomic (e.g. Mossbauer effect, nuclear magnetic resonance, electron spin-resonance, etc.) or optical (e.g. laser, spectral lines, etc.) and many of their combined effects. In some cases, the phenomenon of harmony is also related to resonances, for example, musical harmony which is composed of various mechanical resonances, or the homeostatic balance created by a complex set of selected bio-interactions.

The role of bioelectromagnetics in the resonance phenomena has turned into a "battlefield" in science. The medical facts and their interpretations are mixed with quackeries and medically not proven theories [1]. These unsatisfactory proofs make the "healing electro-therapeutics" highly controversial. For example, electro homeopathy (or Mattei cancer cure [2] [3]) proposes different resonant optical "colors" of electricity to treat cancer. Experts described it as "utter idiocy" [4].

Severe medical doubts make this topic an impossible research venture. The broad legal and illegal medical applications draw attention to this attention-grabbing topic despite its great challenge with multiple unclear details. Differentiating the quackeries from scientifically approved facts confuses the discussion. Unfortunately, these concepts have been adopted and misinterpreted by the non-scientific community, resulting in the development of pseudoscientific beliefs. A further complication is that almost all unscientific explanations include well-proven facts within their unproven or false statements. Unfortunately, these concepts have been adopted and misinterpreted by the non-scientific community, resulting in the development of pseudoscientific beliefs. This further contributes to the poor acceptance of the topic by professionals. The judgment of a great scientist, Stephen Hawking, summarized it: "The *greatest enemy of knowledge is not ignorance*, *it is an illusion of knowledge*" [5]. An example of the misuse of a scientific concept involves mechanical resonance, a condition in which a mechanical system responds with increased amplitude when the frequency of the system's oscillations matches the system's natural vibration frequency. A frequency limit and definite boundary conditions are disregarded when the concept is used to describe pseudoscientific theories. Another frequent "shift" uses the well-proven quantum-mechanical effects in the micro-world atoms and molecules to explain macroscopic bodies. Therefore, the use of resonance in oncological applications requires in-depth investigations to filter out the facts from the pseudoscience. The question is: "Who is the fake one now?" [6]. I try to collect many ideas connected to resonance phenomena, point out the dubious parts, and focus on possible developments.

2. The Pythagorean Harmony

The ancient Greek culture developed the first resonance theory. Centered on the mechanical resonances of a tense string, Pythagoras introduced a set of resonances that explained leading musical harmony in European culture. The Pythagorean school developed mystic numerology by observing the connections between the mechanical resonance of the tense string and its environmental matter (musical sound). Pythagoras created an approach to the vibration of string using ratios of integers. His discovery became the basis of some geometric and musical works, establishing the numerological harmony of musical tuning [7].

When one string is exactly half the length of another string, the notes will have different pitches but will still be in harmony. The interval between the two

notes is called an octave. The Pythagorean tuning system, developed by Pythagoras, is based on a frequency ratio of musical intervals of 2:3, or the "perfect fifth" (3/2). In musical Pythagorean tuning, the power function of the ratio of "perfect fifth" $\left(\frac{3}{2}\right)^n$. The structure forms a scale and the 2^{-p} transposes the scale to the fundamental octave [8]. The perfect fifth can be divided further on the same ratio following the $2^n 3^m$ (where n and m are integers) division rates on the string. This way the Pythagorean music makes the sounds based on the length of tense strings in a scale, where the template is the "perfect fifth" which divides the string by 2/3 portion. Hence, the correct set of tense string vibrations has a $\frac{1}{2^p}\left(\frac{3}{2}\right)^n = 3^n 2^{n-p}$ [8] divisions in musical structure.

The subjective human sense enjoys musical harmony, which does not fit properly with the mathematical construction. A dissonance appears in senses, the "Pythagorean comma," or "wolf fifth". A critical feature appears here: the "dissonance" of the wolf-fifth, a fundamentally psychological rather than based on mathematical objectivity.

The "magic" $\frac{3}{2}$ also appears in other ancient science. Aristotle, a significant influencer of the European culture of ancient times and the middle ages, observed the same ratio between the volumes of the cylinder and its inner nesting sphere, which is valid for their surfaces. Kepler also applied the musical ratio in the cosmos' harmony, forming the cosmic monochord of the universe [9]. Kepler's observation of the planets' distances follows a musical harmony (music of spheres). The proof of this theory, of course, considers the limited possibilities of the observations in Kepler's time.

Interestingly this early mysticism has some real roots in nature, mainly due to the standing harmonic waves formed in the tense string with fixed ends showing $n \cdot \frac{\lambda}{2}$, where n is integer and $\frac{\lambda}{2}$ is the half-wavelength of the formed wave. The hypothesis of applying ancient numerical wisdom in modern physics surprisingly supported the other "Pythagorean quantization". The mathematical apparatus of such modern fields as quantum mechanics [10] and the structure of DNA [11] apply the Pythagorean symmetries. The wave quanta with integers appear in the string theory of the standard cosmologic model [12].

The other Pythagorean discovery is the triplets of the right triangle drive obtaining Sommerfeld's fine-structure constant and show similarities with the quantum Hall effect. It could be applied in the time-dependent quantum mechanics connected to the time-dependent complex nonlinear Riccatti equations [13], and the $\frac{e^2}{c}$ $\left[=\frac{e^2}{4\pi\varepsilon_0 c}\right.$ in SI units] least Coulombic action. The generalized Pythagorean theorem appears in many topics in physics [10]. It also appears in the space-time distances in special relativity [14], and could be connected to optical imaging by the reciprocal values [15]. The applied Pythagorean triplets

are well described theoretically [16] [17]. The applicability's main origin covers the fundamental distance-like values in the Cartesian coordinate system or the law of cosines in any coordinates. However, the similarities of the Pythagorean triplets and numerical string theory with the quantum effects and differential equations do not mean the quantum-mechanical application or relevance of Pythagorean theorems. These similarities are formal. The simple deterministic mechanical concept has no fundamental connection with the probability-based quantum ideas.

3. Therapies with Bioelectromagnetic Resonant Frequencies

The mechanical behavior of the electromagnetic phenomenon is nonlinear in space distances, causing many complications for the first modern scientific investigators, Coulomb and Ampere. The electric and magnetic fields introduced by Maxwell [18] solved this problem by linearizing the forces depending only on the fields and the resting or moving electric charges. These new constructions could only be detected in specific materials with charges and currents and were otherwise insensible to the human senses. The concept of the electric and magnetic field was therefore perceived as a "miracle" by many laypeople, and many pseudoscientific beliefs targeted it. The main controversial "battlefield" is bioelectromagnetism, the effect of electromagnetic fields on living objects.

Heated debates have emerged on the effects of environmental factors on health and on the development of malignancies, for example, induced by the energy transfer networks (like powerlines) [19] [20] [21] [22] [23]. However, the explanations proved controversial and often found to be inconsistent [24]. Broad approaches are discussed in the topics of "electrosmog" [25] [26], "magnetic field medicine", [27], "new biophysical field", "force-free actions" [28], "scalar-wave effects" [29], and "subtle energies" [30]. These topics have created upheaval in the field of bioelectromagnetics, with strong opposing arguments from physical [31] and mathematical points of view [32] [33]. Most of the measured and medically proven but contradictory results in bioelectromagnetism characterize the complex behavior of the biosystems, which has a "Janus face" feature because it inherently depends on internal and external conditions. The same "electrosmog" radiation could be "healthy" or "unhealthy" depending on the conditions [34].

Most of the bioresonance theories involve electromagnetics and/or quantum-mechanical explanations. Nikola Tesla considered resonances as the most general law of nature [35], which focused attention on this topic. Tesla applied electromagnetic resonance in most of his numerous patents, like the alternative current [36] and wireless communication [37], founding a unique bioelectromagnetic view [38]. Tesla worked out a method for electro-therapeutics, using "ultraviolet rays" [39].

The other influence on the bioresonances has a quantum-mechanical origin. The Aharonov-Bohm effect [40] led to new ideas. This quantum-mechanical in-

terference phenomenon may be applied in the concept of the "field-free" vector-potential with possible biological application [41] [42]. The vector potential deals with the influences of the inherent fluctuations that allow the unmeasurable field-effect in a macroscopic spatiotemporal measurement, the vector-potential acts in macro ranges [43].

The "resonance topic" in cancer therapy started with a revolutionary step of optical microscopy, developed by Raymond Royal Rife [44]. The Rifemicroscope had the ultimate resolution at that time [45]. The microscope was able to observe the cellular morphology and changes in cell culture in natural, time-lapse conditions with as high as 31,000 resolution with low aberration, while the standard laboratory microscopes at that time had only 2000 to 2500 [46].

The great advantage of the microscope was its resolution and the possibility of observing the time-lapse dynamics of living microbes [47]. The Rife microscope does not harm the specimens under observation. The microscope's ability allowed researchers to study the processes caused by environmental interactions. The time-lapse facility was an extraordinary chance to study living interacting cells by visualization and registering the dynamics of cells alive over a long time [48] [49] [50]. Recording the time-lapse microscopy movies of microbes excited the researchers of the time. Note, the time-lapsing nowadays remained very popular and used in many microscopic solutions, mostly applying modern, extreme high-resolution live-cell imaging without Rife's microscopy.

Using Tesla's arc lamp idea [51], Rife constructed arc radiation ("beam ray") in an argon-filled glassflask, pumping it with various modulated radiofrequency (RF) power [52], and he used its radiation for microbes under his microscope [53]. He observed "resonant frequencies," where the pathogens will perish [54] [55] [56] [57]. Rife collected these unique frequencies and registered the "mortal oscillatory rate" (MOR) for various pathogenic organisms. The resonance idea spread rapidly among the experts and laypersons, assuming the same "curative effect" in vivo, without proof. The new claim declares the cure of cancer without relevant observations. The rigorous theoretical and clinical studies are nowadays also largely missing. Later Rifemodified the cancer-cure idea, saying that he may devitalize the disease.

After the death of Raymond Rife, a large market developed, using his work to provide false hopes for cancer patients (at this point, the market-related profit-making substantially impacted the field). The new "Rife-machines" do not use plasma radiation. Instead, they apply only minimal current (milliamperes) of various modulated RF carrier frequencies, which promises to kill the cancer cells in the whole body. Most of the devices were utterly deceptive, and while they directly did not harm the patients, those who used these were isolated from the benefits of proven treatments by their firm belief that the Rifemachine helps. More and more publications were available by elapsing time, showing the problems with the original Rife frequencies and its "theory" behind them. The theoretical part was fragile; the experimental results had no explanations, while the

publications did not describe the experimental conditions professionally. The lack of evidence and the presentation of only a selection of favorable cases supposedly treated by Rife resulted in the development of a field of "pseudomedicine" supported by electronics [58] [59]. The fraudulent activities were punished [60] [61]. Such "Rife devices" have figured prominently in several fraud cases in the US, typically centered around the uselessness of the devices contrary to their marketed grandiose claims. In a 1996 case, the marketers of a "Rife device" claiming to cure numerous diseases, including cancer and AIDS, were convicted of felony health fraud [62]. The sentencing judge described them as "target[ing] the most vulnerable people, including those suffering from a terminal disease," and providing false hope [63]. Rife machines have been blamed for the deaths of cancer patients who might have been cured with conventional therapy [64].

Unfortunately, many questionable methods use the "phenomenon" of generating profit from believers without acceptable scientifically and medically approved evidence. Rife devices are currently classified as a subset of radionics devices generally viewed as pseudomedicine by mainstream experts [65]. No evidence was produced [66], and it was declared quackery [67] [68]. The Rife frequency generator is an electronic device purported to cure cancer by transmitting radio waves. Authorities in the UK and the US studied this device: "there is no evidence to show that the Rife machine does what its supporters say it does" [69].

However, the appearance of the bioelectromagnetic resonance needs clarification despite many unsuccessful experiments and sometimes misleading or even falsified data. The mixture of the facts and the hidden false statements using scientific language makes the debate too complicated. Such patented ideas as Lakhovsky's radio-cellular-oscillator [70] [71], Rife'sresonant waves [57] [72], Priore's electromagnetic therapy [73] [74] [75], are unproven in systematic studies, but some positive case reports were published. However, these selected results do not provide enough proof to verify the effect.

On the other hand, the missing proofs do not mean directly that the idea is quackery. Future discoveries may find the missing proofs with new research facilities like Gurwitsch's morphogenesis-based mitotic wave in mitosis [76] [77] [78] and some enzymatic reactions [79]. Gurwitsch's pioneering work has a revision integrating the bioelectric interactions [80] [81]. However, presently we have only indirect proofs in this field as well. Not enough sensitive tools exist to measure the supposed effects [82].

The psycho-effects of otherwise safe (maybe ineffective) methods keep many of these therapies alive, providing a placebo for the patient [83]. The placebo treatment does not mean "no treatment" [84]; it could help with belief. This psychological issue is mostly palliative [85]. The missing efficacy becomes harmful because the patient remains without professional medical care, and the disease may become irreversible.

Low-level, non-stationary magnetic fields have been observed [86] and adopted [87] as a nonthermal electromagnetic effect. One of the essential nonthermal

processes is the so-called "window" effects [88], which shows significant calcium influx to the cell at the low-frequency modulation of radiofrequency around 16 Hz frequency "window", having an optimum frequency and amplitude to interact with cellular membranes [89]. The window effects have some resonance characteristics. The measured frequency dependence varies based on the experimental conditions and could act in a synergistic way with chemical processes [90]. The "window" was measured in multiple power ranges [91]. These experiments were considered to be nonthermal due to the low energy (max5 uW/g energy). The maximum of the active Na^+ flux was observed between 0.1 - 10 MHz [92], which "window" effect could be well explained by the active transport system model in the membrane [93].

4. Controversial "Quantum Resonance" Based on Pythagorean Harmony

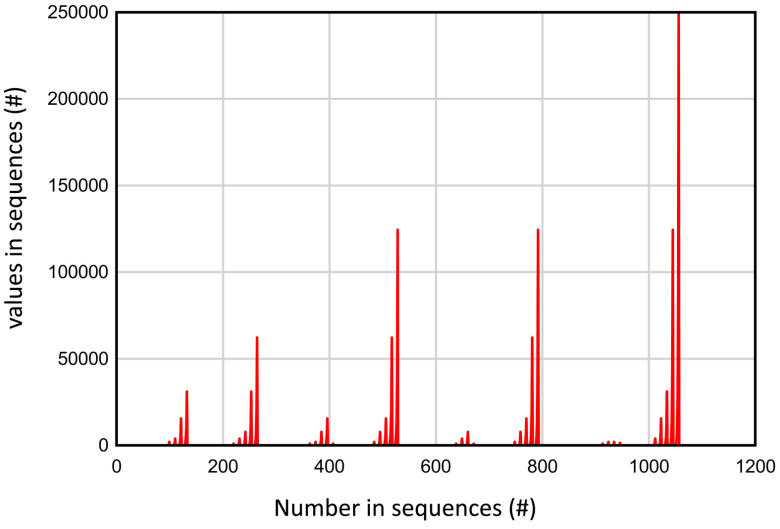
The quantum-mechanical resonances attracted the attention of many researchers. For example, the "orchestrated objective reduction of the quantum state" [94] concentrates on microtubules in the cells; the quantum-field approach of the water [95]. Many publications were devoted to living organisms' health-sustaining coherent, decoherent frequencies (detrimental) [96]. The idea has a root in the interference of waves. The interference pattern could be constructive and destructive, giving the biological rationale of the wave harmony [97]. These facts prompted the application of the Pythagorean wave harmony on strings to explain the resonance frequencies, including the Rife frequency spectrum. This resulted in a shift from the integer-based ancient set of wavenumbers to the quantum-mechanical energy eigenvalues starting from a reference frequency ($f_{ref} = 1\,\text{Hz}$, due to practical reason) set of frequencies, defined by the formula called "GM scale" [98]:

$$E_n = hf_{ref}\,2^n 3^m \left(2^p\right) = \hbar\omega_{ref}\,2^{n+p}3^m \tag{1}$$

where E_n is the energy values of the discrete coherent electromagnetic waves, h is the Planck constant, and n, m, and p, are selected integers [99]. Analyzing the powerdensity of this generated Pythagorean spectrum, it follows a scaling law of $S(f)$ noise density: $S(f) = f^{-\alpha}$ shown in **Figure 1**. By sorted number-sequences of n, m, and p.

This mathematically correct scaling requests in (1) $n = 0.5$ (wolf sound) too, which is not an integer. The Pythagorean musical structure $\frac{1}{2^p}\left(\frac{3}{2}\right)^n = 3^n 2^{n-p}$ [6] limits the "freedom" of (1), so the spectrum differs from the assumptions of [99].

The consequences of the quantum wave in musical harmonic ratio had induced some doubtful research using the "cosmic musical master-code" [100]. The "mastercode" follows the Pythagorean harmony, with an extended anthropomorphic presentation of the human musical sense of harmony. Dubious research explains some fundamental problems in quantum mechanics with the



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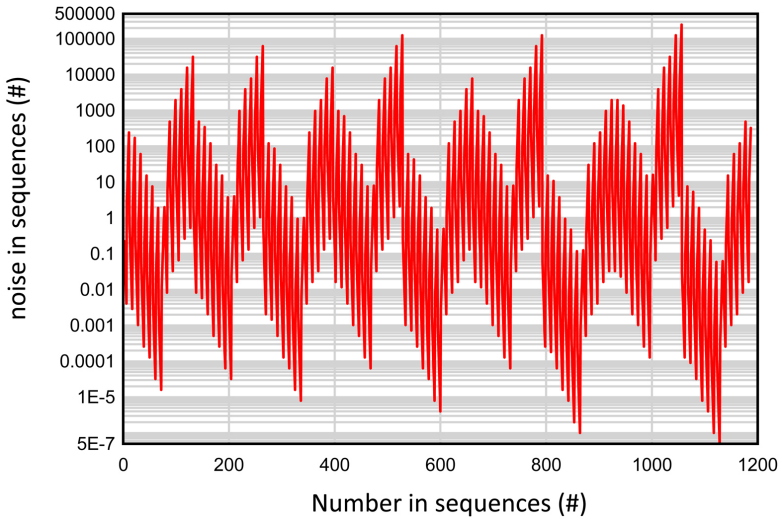

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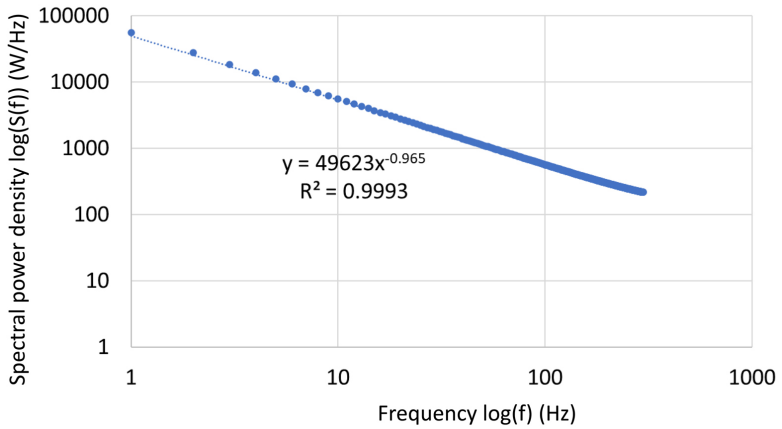

(a)

Figure 1. The frequency spectrum of the Geesink-Meijer "GM scale" (a) The spectrum in frequency; (b) The noise of the spectrum; (c) The $S(f)$ fit with Fourier transformation (FT, $\alpha = 0.965$, Microsoft excel), which practically approaches the pink-noise spectrum [99].

ancient Pythagorean numerology. The descriptions include Bohm's implicate order [101], quantum coherence in living processes [102] [103], and even attempting to explain the origin of life with mineral interactions [104]. The consciousness is described with the help of the generalized Pythagorean musical harmony [105]. The theory also supports such mystique as the afterlife [106].

The theory and its presented proofs have serious challenges:

1) The Pythagorean harmony is valid in a tense string. The waves are formed in fixed boundary conditions, and these determine the waves in a system. What are boundary conditions fixed in this harmony concept? Where are these "strings" which resonate with the Pythagorean scale? How could the tense string waves be formed in the macroscopic cells?

2) The $h \cong 6.6\times10^{-34}\ \mathrm{J\cdot s}$, which means subtle energy by (1). The quantum energy is enough to act in a quantum-mechanical object (like an electron in the atoms). However, the proteins are macroscopic (the cells are even more on a macro-scale) and immersed in the environment with thermal fluctuation in body temperature, which drastically exceeds the subtle energy transfer: $1k_BT \approx 26\ \mathrm{meV} \approx 4.2\times10^{-21}\ \mathrm{J}$ [107]. One of the lowest binding energy in biosystems are the hydrogen bonds in various structures, having 6 - 30 kJ/mol (≈2 - 12 k_BT) [108] [109] [110]; which are 2 - 12 times more than the thermal fluctuation in the living body. How is the energy of "quantum resonance", which is $\approx10^{13}$ times less than the energy in hydrogen bonds, expected to alter the cancer cells? A question also arises: which signal pathway is chosen and which molecules are involved?

3) The description of (1) uses the 1D string vibrations and the wave-forming on the plane sheets [111]. However, the plane waves (membrane resonances) depend on the shape and thickness of the vibrating sheet (boundary conditions) [112] [113] and are not as simple to interpret as is proposed by the analogy of the tense string vibrations. A detailed and correct description is necessary to explain the proposed effects.

4) This quantum hypothesis continues the Pythagorean number-mystique as a mathematical algorithm for coherent quantum frequencies, used to support the Rife frequencies [114]; and the nonthermal electromagnetic interactions [96]. The Geesink Meijer "GM" scale appears to use similar divisions as the cents. It ranks from 1.0 to 1.898 for "coherent" ("GM-scale") and from 0.974 to 1.837 for "decoherent" "GM spectra", with the same twelve divisions of the "octave" [115]. The normalized frequency spectrum of the "beneficial" vs. "detrimental" signals [96] shows a continuation of the spectrum in an extensive range of frequencies. The slope of the beneficial vs. detrimental plot shows a ≈3.4% deviation from the equality of the two opposite effects increasing the doubt about the validity of the hypothesis **Figure 2**.

5) The further dubious consequence of the GM scale is the identical frequency dependence in Hz and GHz regions **Figure 2**. This contradicts the expectations of different mechanisms in these scales. The low frequency is principally active

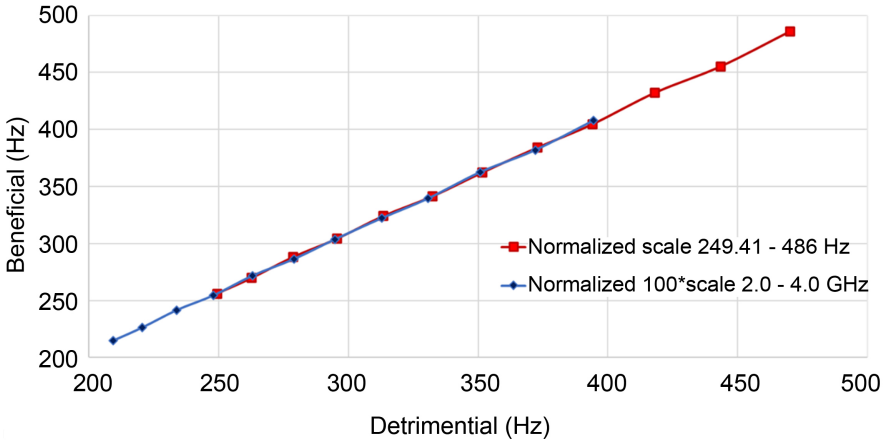

Figure 2. The "beneficial" vs. "detrimental" frequencies of "GM scale" [96]-[101]. A comparison of the GHz and Hz spectra shows complete identical slopes (slope = 1.03, $R^2 = 0.998$).

in the extracellular matrix and the cellular membrane, while the high frequency penetrates the cytosol and changes the molecular processes intracellularly.

6) The fundamental doubt about this hypothesis comes from the harmony itself. The living systems have heterogenic "strings" and "plates" with complex interactions. The existence of these strings and plates resonating in "harmony" is illusory because all the strings and plates have different boundary conditions, so their resonances are far from the same, so their harmony needs much more conditional assumptions than Equation (1) describes. The healthy "harmony" is regulated and controlled by homeostasis, which induces 1/f noise calculated by multiple entropy analyses [116].

7) The data contain 219 and 123 separate biomedical studies for healthy homeostatic and cancerous situations, respectively [117]. The essential request of the statistical evaluation is cohort homogeneity which does not exist in the data for the GM-scale. The vast number of observations collect various experimental setups and use various substances, so these do not fit one unified GM-scale. The data do not belong to the same group of experiments, so their interpretation as a cohort is incorrect. We must have data collection and clinical trials according to international standards to surmount the trap of dubious assumptions.

8) According to the above doubts, the Pythagorean quantum coherence is a proofless continuation of the ancient Pythagorean number mysticism. The Pythagorean vibrating strings concept deals with mechanical conditions in a deterministic way. How does it fit the stochastic probability methodology of quantum mechanics? It is not as universal as quantum mechanics and has no such probability-dependent, stochastic phenomena, which are regarded as the corner point of quantum phenomena [118].

5. Doubts on Cancer-Specific "Resonant Harmony"

The health-supporting and detrimental signals from only a few Hz to THz frequencies are included in the massive set of "resonant" frequencies [119], mostly

corresponding with Rife-frequencies results. Decoherence as the hypothetical cause of cancer [120] is also a noteworthy hypothesis. However, there are also numerous open, unanswered questions:

1) Cancer cells are "softer" than their normal host cells, and their membrane tension increases [121]. At the same time, their tumor is "harder" due to the place-demanding proliferation. Cancer elevates the lateral motility of membrane compartments [122], and at the same time, the membrane becomes more rigid in the perpendicular direction [123]. How do these cellular effects act positively or negatively on the resonances of tumor cells?

2) The tumor cells have lower membrane potential than their healthy host cells [124] [125], having shallower potential-well. Consequently, the probability of fixing the wave function inside the well is low (the tunnel effect dominates). How does the strict spectrum form?

3) The extracellular matrix in the cancer cells' microenvironment is highly disordered [126] [127] because the tumor cells break their networking connections (these are primarily individual, "autonomic" cells). How could resonances modify the harmony between them?

4) The minimal change which we need to modify the cellular structure is the transition of the unfolded state of polypeptides to the α-helix, when the entropy changes (decreases) by $\Delta S_{fold} = -1.38 \times \ln\left(6^{20}\right) \times 10^{-23}\ \mathrm{J/K} \cong -4.95 \times 10^{-22}\ \mathrm{J/K}$ which means the change of the internal energy $\Delta U = T\Delta S_{fold} \cong 1.4 \times 10^{-19}\ \mathrm{J}$ [128]. This is considerable energy compared to E_{quant} from (1), where $E_{quant} \cong 10^{-30}\ \mathrm{J}$ up to f is in kHz-region. From where does the energy come? Note, the THz frequency or higher (like optical) would be enough to provide the missing energy, but the RF range can not.

5) Cancer cells differ by size and shape from normal cells [129] and from each other [130] and even vary by metastatic potential [131]. How could the resonances with a single frequency modify these objects with various forms and conditions?

6) The beneficial and detrimental frequencies are linearly connected. The general biological frequencies [117] differ from cancerous frequencies in **Figure 3**. An explanation is needed, why are they generally "beneficial" frequencies not beneficial for cancer, and the opposite is that the systemic noncancerous "detrimental" frequencies differ from the detrimental resonances of cancer? Does this mean that the cancerous state is not detrimental?

7) Multiple measurements also show the effects of various parts of the cells in low-frequency regions. These changes are chemical and have nothing to do with such energy described by (1). These effects are induced by the electric field interaction in the classical energy exchanges, such as the Drude-model, frequency dispersions, or charge movements. These exchange energies are much higher than the supposed quantum-mechanical effect in (1). According to our current knowledge, the quantum description of the macro-particles and giant molecules like proteins or DNA is missing. Consequently, the wavefunction and the eigenvalues used in (1) do not describe the macro-objects in such small energies as

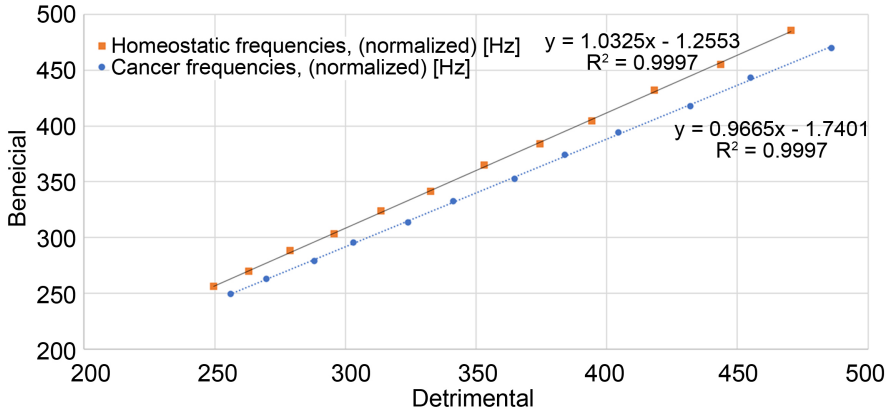

Figure 3. The normalized "beneficial" vs. "detrimental" frequencies (low-frequency spectrum) in cancerous and healthy states. It looks that the "detrimental" frequencies in a healthy state are not parts of the cancerous "detrimental" frequencies, and those frequencies which are "beneficial" in a healthy state are not parts of the beneficial frequencies of the cancer states showing the difference of the "detrimental" categories. A question arises: What do the defined "detrimental" and "beneficial" categories mean?

supposed in (1).

6. The Clinical Renewal of the Rife Concept

The resonant frequencies' concept was renewed about ten years ago [132]. The "Rife machine", which uses galvanically coupled current through the body from the electrodes in hands or feet, had been modified for under tongue electrode, providing high RF-frequency (27 MHz) as a carrier and delivering the "resonant frequencies by amplitude modulation of this carrier [133]. The in vitro experiments based on the historical roots [134], including Rife, Laskowski, and others, were used to prove the subtle energy application's clinical effect [135]. The method could also influence the effect of the cancer stem cells on chemoresistance [136]. A remarkable effect is shown for brain metastases on mammary carcinoma [137] and applied to one of the great challenges of the current oncology approach to hepatocellular carcinoma [138]. The method looks like a 'shift again' [139] after the long and complicated hectic changes in resonant frequencies" history.

The protocol of the treatment is simple and ultimately differs from GM-scale. The patient receives the electrode intra-orally, and nothing else is necessary for the process. The applied modulation frequencies are mainly in audio, but in some tumors, it goes up to 100 kHz range [140]. According to the protocol [140] I visually show the spectra for different cancer locations (**Figure 4**).

The patient receives every individual frequency for 3 s and sorts up to the higher values. Spectrum modulation frequencies are provided. The entire therapy session has 1 h duration, where the scan of frequencies is repeated when all the "prescribed" resonances were given [141] (**Figure 5**).

Together with the questioned, unknown molecular mechanisms of the method, the technical realization of the treatment has many challenges and doubts.

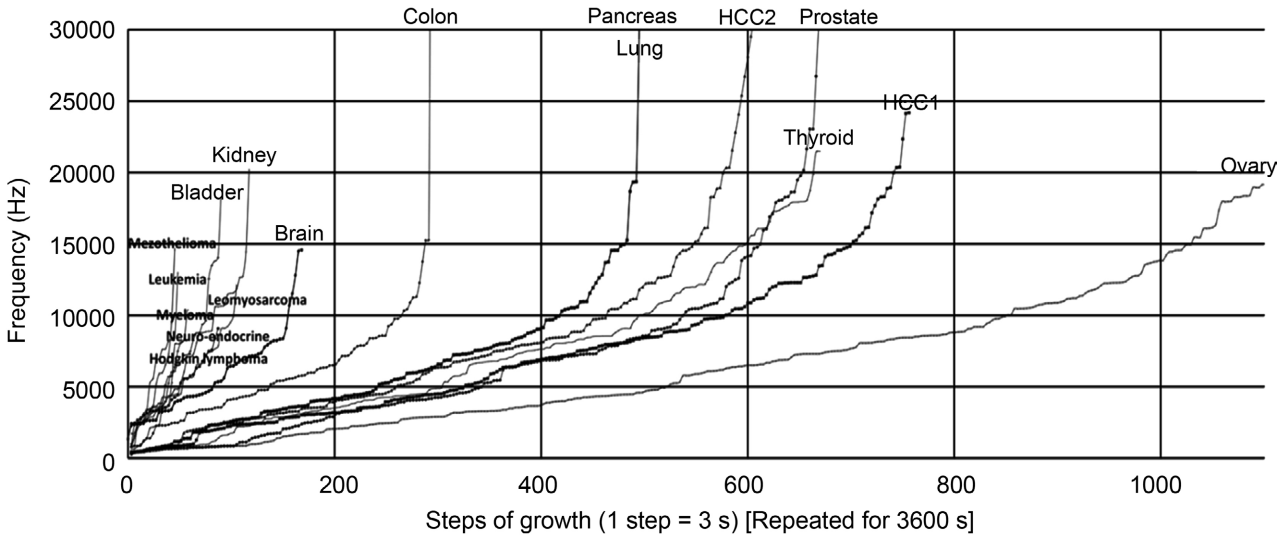

Figure 4. The frequency spectrum vs. time of the treatment in different diseases. The discrete points of the frequencies subsequently increase by 3 s constant state. The 60min duration of the treatment involves repetition of the discrete spectrum until the end of the treatment period.

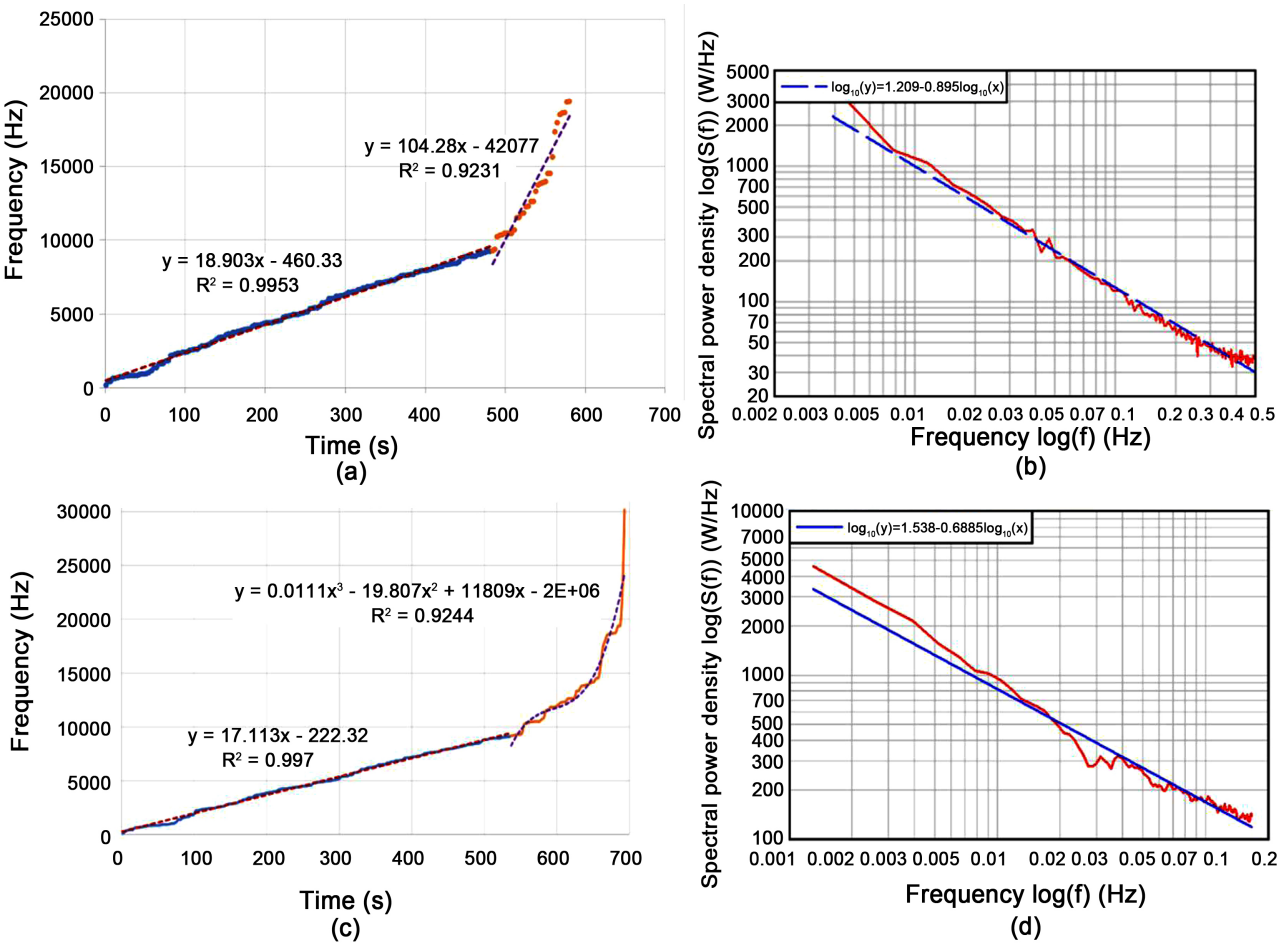

Figure 5. Example of breast treatment frequency applications. (a) the discrete frequencies by time (1 step = 3 s) [142]. Treatment repeats it until 60 min; (b) the spectral power density $S(f)$ fit by FFT ($\alpha = 0.895$, Dplot); (c) Breast treatment in other publication; (d) its spectral density by FFT ($\alpha = 0.6885$, Dplot).

1) Only a single electrode, the intrabuccal spoon-shaped one, exists immersed in a saline environment. This single electrode does not form a definite RF electric circuit. The missing fixed RF circuit occasionally closes capacitively, coupled to the actual, uncontrolled environment of the patient [143].

2) The patient receives uncontrolled minimal (subtle) current intensity (μA) on an uncontrolled path of the current flow. How does it act selectively on the malignant cells throughout the whole body?

3) Notably, the shown SAR is ≈5 W/kg which is shown in the many independent parts of the body [143], implying the homogeneous SAR in the entire system. In the case of a 60 kg patient, it requests tremendous 300 W power homogeneously distributed into the body. From where this extreme power is coming? It is not possible to introduce such high power intrabucally, and the power supply is via a rechargeable battery.

4) There is no information on how the frequencies were chosen. Was it measured (not published) or is there a principal hypothesis? The frequency's power density has a slope of ≈0.6 - 0.8 on the double logarithmic scale. A publication referring to the treatments of breast cancer, hepatocellular carcinoma (HCC) [142] shows inhibited cancer-cell proliferation by specific modulation frequencies compared to random frequency reference. Frequencies differ by the individuals [140], while the power density fits well to the different diseases: for breast cancer $S_{breast}(f) \cong 1.533 - 0.8797\log(f)$; HCC: $S_{HCC}(f) \cong 1.554 - 0.8790\log(f)$; and the random frequencies although the method of randomizing the frequencies was not published) $S_{random}(f) \cong 1.598 - 0.8754\log(f)$.

5) Technical details are missing about the modulation depth, accuracy of the frequencies, and the applied voltage.

6) The patient's impedance is very personal. No information was given about how it was tuned for personal parameters.

7) The in vitro and in vivo applications have no adequate technical description of the method, and it appears as if these have much higher energies per unit mass than the subtle (nonthermal) energy in human applications (≈1 W/(whole-body)). The cell sizes and shapes differ in vitro, in vivo, and ex vivo conditions [144] and significantly depend on their tumor microenvironment [145] and the signaling processes [146]. How can the resonances be compared?

8) Case reports show the efficacy. However, the reports on the clinical trials which were started 14 years ago [147] [148] are not available on scientific or academic platforms. The design of a new clinical trial is also announced, but no further information is available [149].

Despite the dubious theoretical concepts, the *in-vitro* and *in-vivo* experiments and the clinical data support the resonant phenomena. In the following, I am trying to give a possible stochastic explanation of the observed results.

7. Stochastic Processes

The living systems form a complex dynamic equilibrium that allows adaptation

to the environmental conditions and internal regulative actions on broad scales in space and time [150]. The dynamic living structures perform random stationary stochastic self-organizing processes. Fractal physiology describes the system with interconnected self-similar spatiotemporal composition by fractal structures in space and time [151] [152] [153]. Moreover, the fractal physiology approach has practical medical applications in diagnoses [154] and therapies [155].

The conventional deterministic descriptions are insufficient to explain the observations, and stochastic processes determine the living objects [156]. The deterministic description is valid only in broad averages in space and time. The averages are macroscopic and could mislead microscopic research, which is necessary for resonance phenomena. Understanding the biological dynamism requires stochastic methodology, using probability "decisions" in all steps, and going over transition states that frequently have enzymatic assistance. The often ignored homeostatic balance governs the living processes in all spatiotemporal scales. Involving homeostasis in explanations is mandatory in order to understand the living complexity [157].

Due to the stochastic phenomena, the signals of the diagnostic parameters of the living processes fluctuate around the average of the band of acceptance signal level. The dynamical changes of microstates of the processes vary the fluctuations, regulated by feedback mechanisms. The negative feedback is the easiest way to regulate the desired values because when it stimulates the suppressor, the promoter limits the changes when it increases. The positive feedback triggers the development of a dynamic step, using the suppressor-promoter actions to reach a new equilibrium state. The overlapping signals and their interconnection create noise. The relatively constant noise time averages $\langle D_i \rangle$ of the microscopic diagnostic states D_i. and standard deviation (σ_{D_i}) varies according to internal and external conditions. The homeostasis controls the complete spatiotemporal setting, regulates the order of noise structure, and keeps the signal within a tolerance band around the l_{D_i} (**Figure 6**).

The subject is healthy when the homeostatic control faultlessly keeps the l_{D_i} bands. Fluctuations $f_{D_i} = D_i - \langle D_i \rangle$ carry the details of the microscopic changes. The change of regulative processes drastically varies the f_{D_i}, delivering information about the transformation of the microscopic interactions. The decomposition of the dynamically varying signals to periodic components (Fourier transformation) allows the signals' frequency, amplitude, and phase changes as components of the "noises". The noise varies when the immune system develops new functions by "learning" to fight against pathogens. The variation could be observed in cancer development, too [158]. Healthy dynamism correlates with metabolic circles and other fundamental living processes. The emitted (measured) fluctuation components characterize the time-set of different interactions and energy exchanges, showing a correlation of the signal with its earlier value at time-lag τ. The time delay describes the similarity of the signal parts when the exact microscopic change happens in the repeated molecular

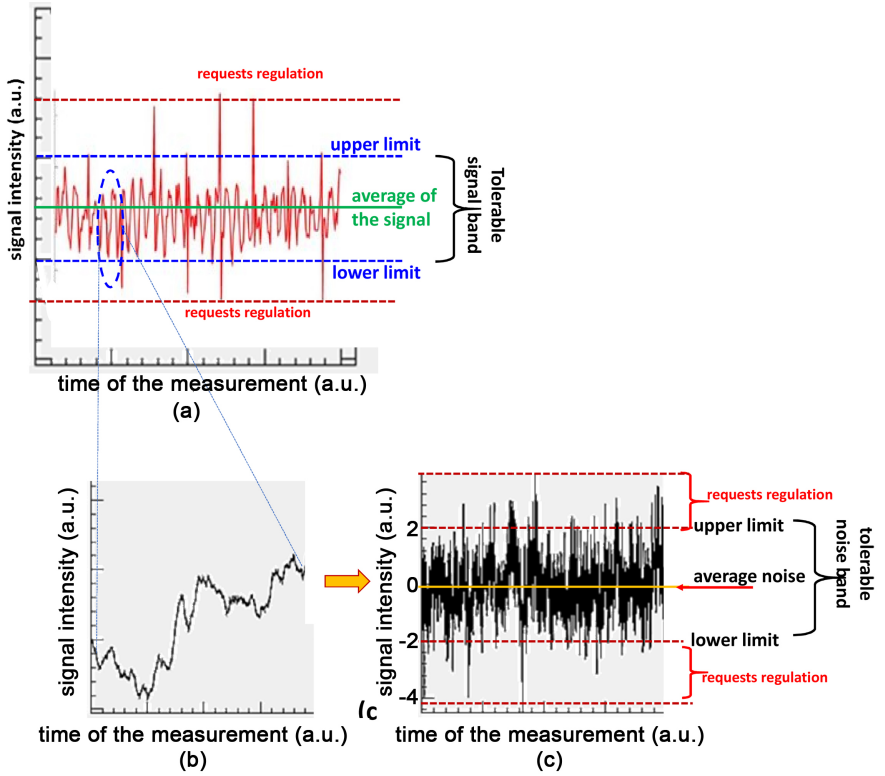

Figure 6. Example of a bio-signal and its noise. (a) the measured signal (b) the enlarged part of the signal, (c) the signal's noise. The usual approach considers the average as the value of a measurement, despite the time dynamics of the signal and the standard deviation being different. The homeostatic control keeps the signal in a tolerable band in equilibrium, and the noise must not exceed the tolerance limit.

signal pathways. The timelag of the autocorrelation function informs the dynamism of the microstates.

The homeostatic balance determines the correlating set of signals involved in the biological changes [159] [160]. The autocorrelation shows the preferences of possible variants of the molecular reactions [161], selection of their timing, and ordering for the desired signal-pathway or enzymatic actions. The frequency-dependent power density spectrum $S(f)$ is a fundamental characterization of the stochastic signals.

The commonly studied simple noise is Gaussian (the amplitudes have normal distribution). The power function of the Gaussian noise is self-similar through many orders of magnitudes showing a simple power function with α

$$S(f)=\frac{A}{f^{\alpha}} \tag{2}$$

As a consequence of the self-similar, self-organizing processes, the $\alpha=1$ ($1/f$ noise or pink noise) appears in the timing of healthy life's dynamism [162], [163]. Self-organizing happens in structural and time arrangements [164] and dynamically regulates the processes in the living matter [165]. Halving or doubling the frequency carries an equal amount of noise energy in the $1/f$ noise,

which has some similarities with musical harmony indeed. The self-organized symmetry of the healthy living system transforms the white noise into pink [166], forming the most common signal in biological systems [167].

8. Effect of Low-Frequency, Low-Intensity Intrinsic Excitation

The literature on cellular resonances concentrates on the low-frequency electromagnetic field (LFEMF), which appears in most of the technics of cancer-specific resonance considerations. Numerous reviews [168] [169], and articles report the response of biological matter to LFEMF [170] [171] [172]. The current expectation is that the periodic intrinsic signal of the low-frequency region is biologically active. The earlier model approximations conclude that external excitation with low frequency is not able to make any effects connected to the cellular membrane. The early models assumed that changes in the field strength result from fluctuations of charges on both sides of the cellular membrane, and this fluctuation completely overwhelms the external excitations [173]. The thermal noise fluctuations at the cell membrane exceed any possible LFEMF-induced signals by some orders of magnitudes [173] [174], so thermal noise limits the electromagnetic influences.

Following the method of symmetrical components (zero-mode) of noise [175], a successful model was developed [176]. The noise of electric current mostly follows a directional symmetry between the electrodes. The zero-mode is a noise-sequence of the RF current inducing electrical energy of the cell-membrane capacity and has a uniform potential in spherical symmetry on the membrane, despite the unidirectional current [176]. The low-frequency zero-mode of noise enables the effect of the subtle external excitation in a relatively high thermal noise environment around the cells [177]. The zero-mode noise-sequence excitation produced by an external periodic signal is symmetrical around the cell.

The complete symmetry required in order to induce a pure zero-mode field at a single cell using outer field generators is impossible because most applied external fields are unidirectional. However, there are self-induced and non-direct methods of constructing zero-mode noise components by applying external energy. Dynamic changing of the extracellular matrix (ECM) composition induces ionic currents producing zero-mode noise around the cell. The thermo-diffusion offers another possibility of zero-mode noise. It could be achieved by capacitively coupled electromagnetic field within a specific frequency range [178] [179] [180] provided the RF current is able to penetrate directly into the cytosol.

Only negligible field penetrates the cell in low-frequency RF current (<10 kHz). The ECM absorbs the vast majority of the energy at these frequencies. The deviation of current flow leads to thermal gradients (thermal currents) from the ECM to the inside of the cell [181]. This thermal current also carries ions through, leading to thermo-diffusion, thus creating the symmetric electric cur-

rent, which induces a zero-mode noise in the cell membrane. Both methods generate a centrally symmetric effect by the ionic and/or thermal gradient through the cellular membrane (Figure 7); therefore, even small fields with zero-mode components could elicit biological effects.

The isotropic membrane appears as a condition of the symmetrical zero-mode noises. However, all cells have anisotropy on their membranes, especially the unhealthy cells (like malignant cells). Here various membrane segments with different electrical properties exists, allowing additional ionic exchanges. The anisotropy increases the non-zero noise mode, having less possibility of direct excitation with signal amplification of the membrane by ion-diffusion. In these conditions, thermal diffusion and its assistance for ionic exchanges remain the option to produce zero-mode noise.

9. Stochastic Resonance

The resonant behavior of stochastic processes is a noise-guided phenomenon [182]. Adding noise to an external deterministic signal of a nonlinear system produces a stochastic resonant (SR) output. The processes in living objects are inherently nonlinear and have bifurcative and probability-determined (stochastic) decisions of the promoter-suppressor actions at all levels of the organism [183]. The anharmonic factor of the potential well of molecules does not allow deterministic decisions. The applied external signal modulation is intended to go over the energy barrier $\Delta E(x)$ between the targeted initial substrate material (S) and the final product (P). The amplitude A of periodic external signal is small compared to the internal noises of the system, and so the provided formation does not become compelling enough.

Nevertheless, considerable amplification of the weak periodic signal could be

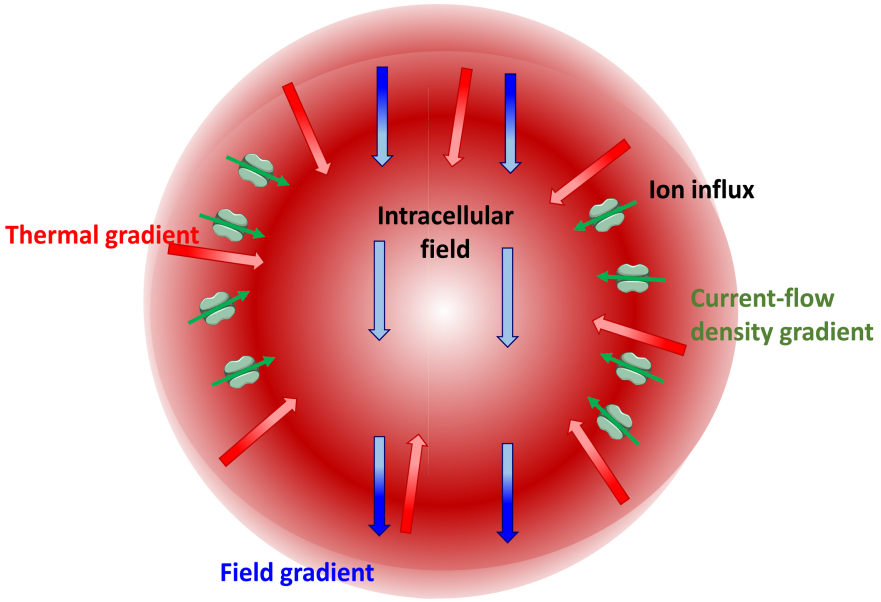

Figure 7. The various gradients at the cell membrane created by the RF-current.

observed by SR, depending on the strength of additional external noise to the intended excitation signal (Figure 8). The SR is only possible in nonlinear systems like living matter when the exciting signal is "noisy". In the models and also in a majority of the practical situations, external or internal Gaussian white noise [184] [185], pink noise [186], Gaussian colored noises [187], or non-Gaussian noises [186] [188] accompany the specific periodic signal.

The signal-to-noise ratio (SNR) amplification has a broad peak in SR conditions, depending on the noise intensity [189] (Figure 9).

The optimal noise intensity appears in the maxima of SNR. When the external noise level or the external periodic signal is kept fixed, the SNR has a saturation of increasing frequency or noise intensity, respectively [190]. However, the residence time intervals between consecutive signal peaks have SR peaks depending on the noise intensity or frequency of the external signal [190]. The SR peak

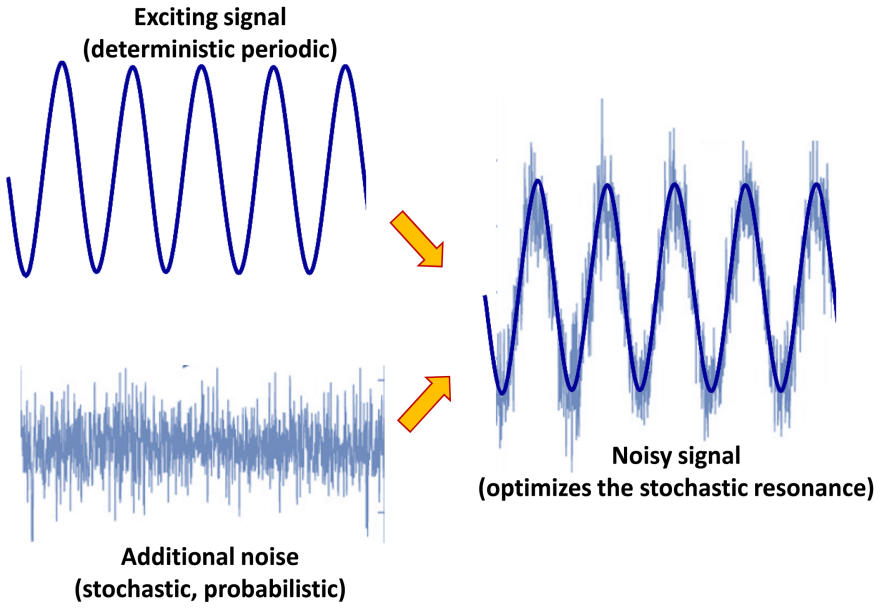

Figure 8. The mixture of the deterministic periodic signal with noise. The resulted "noisy" exciting can induce optimal stochastic resonance.

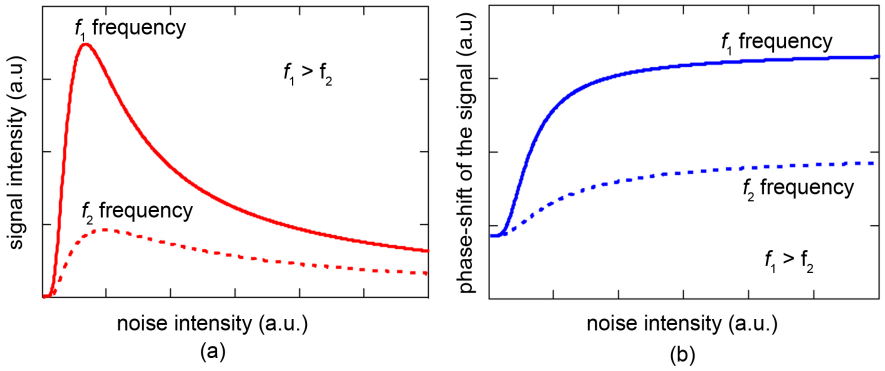

Figure 9. Noise dependence of the parameters of stochastic resonance. (a) Signal intensity. (b) Phase shift.

limits the lower and upper levels of SNR, creating a window of the periodic frequency at constant noise. The internal noises adapt to the complex living system by a negative feedback correction of the optimal noise [191] [192]. The optimal noise induces the maximal SNR, dominating all other states. When the noise intensity deviates from the optimal, the signal weakens. The resonant signal obtains its maximum at some noise intensity, which makes the coherence of the multiple resonating units easier, creating feedback driven by the collectivity of the complex system. The optimizing driving force creates collectivity, which surmounts the individual needs of the cells.

The cell waives a part of its energy for collective utilization in exchange for some shared services and enjoys systemic functions connected to its alimentation, optimal survival with the lowest energy consumption, and overall surveillance against pathogens and other invaders. The collectivity works like some kind of democracy [193] within the tissues. The cell became a part of a network exchanging information and materials as well, and in case of damage, the injured tissue has immediate help from its environment. Cancer follows the opposite way [194]. Its state is a "dismantling of multicellularity" [195], and the cellular collectivity disappears [196]. This development is similar to atavism [197]. In this way, cancer development opposes the collective driving force, its "Achilles-heel" [198]. While the collectivity emits pink noise [116], the cancer cells deviate in their nose spectrum.

The applied single, noiseless frequency excitation was declared effective in various tumor-specific resonance studies [132] may use the internal noises for SR. However, the internal noise differs between healthy and cancerous emissions. The SR is sensitive to the noises, allowing its tuning to the optimal conditions. Different noise spectra develop a variation of the amplitude maxima of resonant frequencies. The original Rife studies [54] [55] [56] [57], used an argon-gas-filled arc-lamp as the source. It differs from other cancer-specific resonant descriptions because the arc-discharge provides white noise for the carrier frequency and improves a well-formed SR's probability.

The enzymes execute the molecular biological changes. Most intra and extracellular molecular reactions have a catalytic boost by enzymes to ease the reactions by transition states and the chemical reactions [199]. A simple, early model, the Michaelis-Menten enzyme model [200] (MME), describes the dynamism of the processes where the quantum mechanical rules govern the transition states [201]. The transition changes the cluster configuration and activates the transitional complex [202].

The MME description involves an enzyme (E) starting the formation of the product (P) from a substrate material (S) through a transition state (E^*) with different conversion rates from S to E^* for progressive and reverse C_p, C_r, rates respectively, and finally from E^* to P with C_f.

$$E + S \underset{C_r}{\overset{C_p}{\rightleftarrows}} E^* \xrightarrow[C_f]{} A + P$$

The first step from the substrate to the transition state is reversible, and the

conditions drive its balance in a negative feedback loop while getting the final product is an unconditional change, the result of the positive feedback process:

The enzymatic processes regenerate the original conformal state of the E enzyme for reuse in a catalytic way. The E^* state has two sub-states (E_1^* and E_2^*) in the reaction: the $E_1^* = (ES)$ complex transforms to P product, via $E_2^* = (EP)$ complex, while the enzyme transforms back to E state at the end of the process. Like all reactions, chemical activity steps are reversible; the progress $\leftrightarrow$ reverse interaction rate balances all steps. The production mechanism must have positive feedback to force P product from the S substrate and shift the equilibrium to a definite direction. The driving force is usually the standard environmental living condition that ignites and controls the process. After finishing the production, the enzyme returns to its initial conformal state and may restart the action. This form of a loop ("catalytic wheel" [203], **Figure 10**), is driven by negative feedback.

The wheel model describes a cyclic catalytic reaction with two conformation states of the process's speed, described by a steady-state technique [204]. The catalytic wheel decreases the energy barrier (activation energy E_a) between the substrate and product. The E_a has thermal (enthalpy factor) and nonthermal (entropy factor) components, and the change of the activation energy (ΔE_a). The subthreshold signal induces SR resonance which causes modification even in single cells [205], controlling the gating membrane channels and selecting ions, and molecules' entry to the cytosol [205]. While experimental general Arrhenius

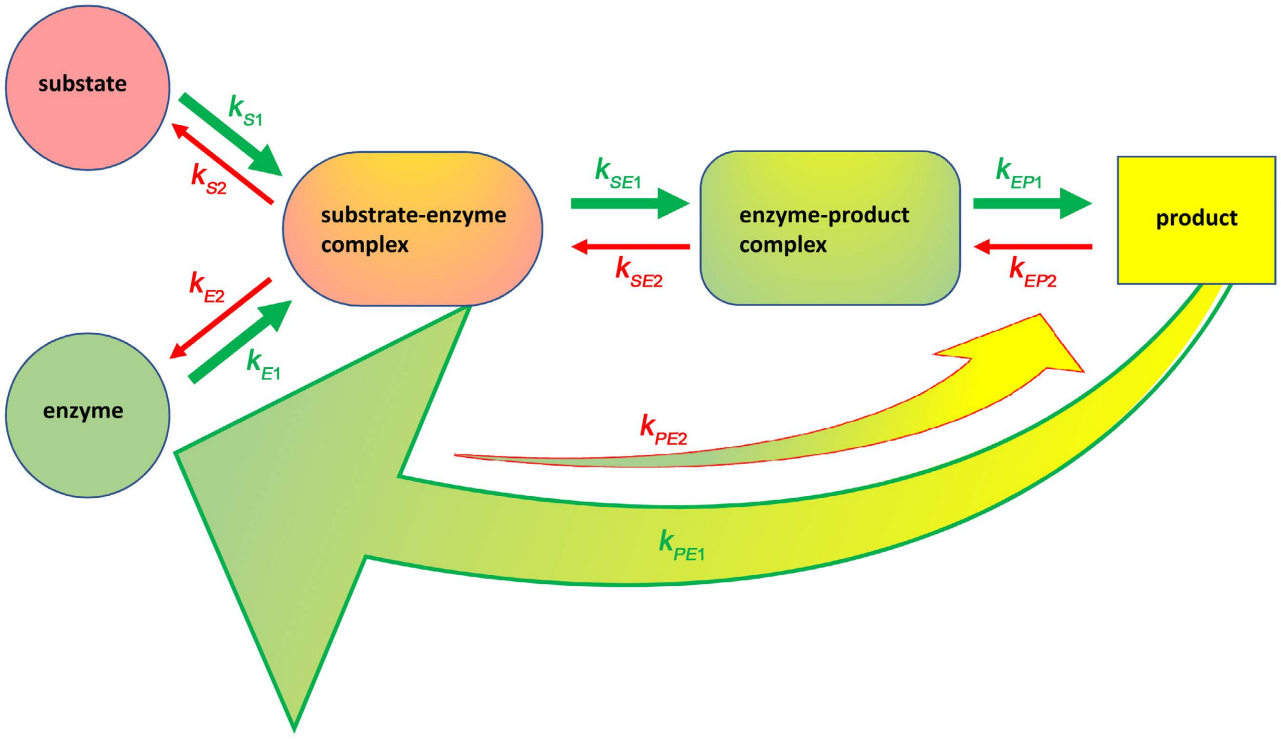

Figure 10. The enzymatic changes during the $S \to P$ transformation. The well applied ECC conditions drive the relation $k_{S2} < k_{S1}$, $k_{SE2} < k_{SE1}$, $k_{EP2} < k_{EP1}$ and $k_{PE1} < k_{PE2}$, so the "wheel" works in one direction, by the Michaelis-Menten process.

law considers a single step jump over the E_a energy barrier, in real processes, the substrate state never transform into products in a single direct step [206] [207], [208]. In this transition, the thermal and electric effects have similarities, unifying the phenomena in a complex unit [209]. Additionally, a typical quantum-mechanical phenomenon, the tunneling effect through the barrier, could modify the transition [210].

The electric field of various electromagnetic signals could actively ignite, modify or block the enzymatic wheels by electro-conformal coupling (ECC, [211] [212]). ECC uses oscillatory SR stimulation to promote the transition of the substrate to the product [213]. The SR controls the probability of the $S \to P$ enzymatic process fixing it in the homeostatic dynamic equilibrium [214]. The environmental thermal noise drives the SR providing energy to this process by the Brownian engine [215] [216]. A periodic electric field may convert the accessible energy-producing transports to chemical reactions coupled through enzymatic processes [217]. The ECC rectifies the thermal fluctuations, driving one-directional dynamics [218] [219], representing a "ratchet" like behavior pumping the processes in one direction only, blocking the opposite turn. The thermal fluctuations, together with the electric noises of the incident signal, provide the available free energy [218]. The thermal energy is high: the ATP hydrolysis has $\approx 10^{-16}$ W, while the thermal factor of dynamic molecular scattering provides 10^{-8} W [220]. The Brownian engine processes work with irreversible thermodynamics with an external periodic perturbation [221]. The thermal components of the micro and macro environment of the tumor cells determine the ECC. When the noise is thermal (white), the ECC has an optimal temperature, but in colored noise (like $1/f$ noise) conditions, the temperature dependence is weaker.

A considerable number of enzymes and enzymatic reactions exist in human biology. The cancer metabolic pathways alone have many enzymatic processes [222] [223], which is a small part of the complete number of enzymes involved in various homeostatic bioreactions. The complexity makes the huge adaption of the system to environmental changes possible when the homeostatic network substitutes a missing process with others. The enormous number of enzymatic reactions determines the number of SR resonant frequencies. Due to the noise dependence of SR, the actual resonance sharply depends on the reaction's environmental temperature and the excitation signal's noise. Consequently, the same bioreaction may have various exciting signals for effective and optimal SR. Complicates the selection of SR that the excitation could also be effective on other nonlinear bistable structures, like the activation of voltage-gated ion channels.

The electrically generated subthreshold stimuli affect the transition state of molecular reactions in various biological processes [224]. One of the explanations of the Rife resonant frequencies could involve the SR phenomena. However, in this case, the resonant frequencies express a dense spectrum. It has as

many resonances as enzymatic reactions that exist in the target. However, another request is to drive the cancer cell's cell death when we do not expect prompt necrosis. The SR amplification has to be multiple, with steps of the signal pathway involving different enzymatic processes and resonances. The complexity offers multiple signal variants, which could direct the pathway to the different final results.

Consequently, the stable solution needs a set of SR frequencies in an appropriate time set. The networking has chain reactions through the signal pathways. The subsequent reactions in the chain define the order of the necessary enzymatic action, which can be modified by external signals when their autocorrelation supports the reaction sequences. The optimally chosen exciting signal with properly fitting autocorrelation can drive the ordered chain reaction with subsequent SRs [225].

10. Conclusions

The enzymatic stochastic resonance defines specific resonant frequencies [226] [227] on the molecular level. The stochastic resonance (SR) describes the interaction of a deterministic subthreshold signal and a fluctuation (noise) spectrum. The phenomenon inherently depends on temperature. The resonant frequencies of neuronal-like healthy and cancer cell membrane channels differ and are excitable [228]. The SR may explain the Rife frequencies. The response to weak external electric fields by definite modulation frequencies could remain active far below the thermal noise limit and ignites some molecular processes by the stochastic resonance. The number of resonant frequencies acting in the cellular processes is at least as many as enzymatic activities. Multiple conditional factors modify the resonance and the frequency of the peak, producing a vast number of different resonances.

Additionally, the SR depends on the temperature and pH in the cell's microenvironment. Furthermore, the cellular structure (like size, form), state (like age, stress), and dynamic development (like chemotaxis and cellular division) certainly affect the resonance and shift or even block the resonant frequency. The size of a studied group of molecules offers a typical size dependence of resonances, including harmony between the group members [229]. The intercellular interaction changes the resonances and multiplies the observable resonant peaks. The modulation excitation of membrane rafts [230] [231] considers this possibility with a well-defined spectrum of modulation frequencies [226] [232]. The resonant reaction complexity operates in a network of interactive intra- and extracellular functions. The interconnection of the intracellular complex multi-pathway feedback loops and the multicellular interactions does not allow for the division of the resonance into two distinct "detrimental" and "beneficial" categories. The biological complexity does not permit the black-and-white categorizing and does not allow to deterministically determine that some resonances are healthy and some are not. The "beneficial" signal pathways may work "de-

trimentally" among various tumor microenvironment conditions. All the participating molecules of the complex network have a "double-edged sword" quality, having optimal molecular reactions in a narrow range of conditions. The molecular change presents deterministic-like processes only when we form a large average of the considered parameters on the macroscale. The microscale offers only probabilistic considerations. The apparent deterministic Pythagorean harmony of numbers is valid only in macroscopic averages, but the resonance is microscopic. The explanation of molecular resonance processes incorrectly describes the phenomena in a classical deterministic way.

Electromagnetic medicine represents a new modality, using molecular biology for therapy [233], including oncology [234]. The molecular excitation by using resonances [235] has enormous opportunities. Some bioresonances, like cyclotron resonance [236], are well proven and hypothesized for new kinds of vaccination [237]. The antitumoral vaccination forces tumor-specific immune reactions ignited by thermal and nonthermal effects of nonionizing RF radiation. Bioelectromagnetismactivates both the innate and adaptive immune system [238], promoting the abscopal effect [239] [240], and becomes a part of the complementary clinical therapies [241] [242]. However, presently our knowledge about bioelectromagnetic resonances is somewhat limited. Rigorous theoretical and experimental investigations with randomized prospective clinical studies are mandatory for the further clearance of the cancer-specific resonant frequencies.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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