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Stimulation and Control of Homeostasis

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Abstract

Healthy homeostasis is a principal driving force of the dynamic equilibrium of living organisms. The dynamical basis of homeostasis is the complex and interconnected feedback mechanisms, which are fundamentally governed by the nervous system, mainly the balance of the sympathetic and parasympathetic controlling actions. The balancing regulation is well presented in the heart's sinus node and can be measured by the time-domain heart-rate variation (HRV) of its frequency domain to analyze the constitutional frequencies of the variation. This last is a fluctuation that shows $1/f$ time fractal arrangement (f is the composing frequency). The time-fractal arrangement could depend on the structural fractal of the His-Purkinje system of the heart and personally modify the HRV. The cancers gradually destroy the homeostatic harmony, starting locally and finishing systemically. The controlling activity of vagus-nerve changes the HRV or the power density spectrum of the signal fluctuations in malignant development, presenting an appropriate control of the cancerous processes. The modified spectrum by a non-invasive radiofrequency treatment could arrest the tumor growth. An appropriate modulation could support the homeostatic control and force reconstructing of the broken complexity.

Keywords

Homeostasis, Vagus Stimulation, Heart-Rate Variability, Immune-Stimuli, Cancer, Time-Fractal Modulation, Bifurcations, $1/f$ Noise, mEHT, Personalized Therapy

1. Introduction

Homeostasis is the vital basis of the dynamic stability of living organisms. The network of negative and positive feedback reactions creates the backbone of complex regulatory processes. The synergy of chemical and physical actors generates homeostasis in a stochastic harmony. The water is a mandatory constituent. The aqueous electrolytes provide the active fundament of various changes in the living systems. The water molecules participate in the harmonization of the complex processes in the separated solutions. The cellular lipid structures (membranes) and some specialized tissues divide the electrolytes, but at the same time, these surfaces regulate most of the chemical reactions for living equilibrium by intensive dynamic processes of various ionic exchanges and electromagnetic forces.

The control of the stochastic regulatory processes has highly self-organized accuracy creating the appropriate products, but some perturbances could disorient the standard mechanisms. The homeostatic system has a variety of tools to correct errors. A significant challenge arose when the collaborative networks were disrupted, and the natural processes could not correct this fault. Such complication happens in the development of malignancy, driven by the unicellular individualism of the involved cells. The malignant structure breaks the multicellular organization (healthy networking). The autonomous cells adapt to the challenges and avoid homeostatic control. These cells hide their erroneous structure, imitate a wound, and force the homeostatic control to heal, support them [1]. This activity changes the micro and macro environment of the malignant cells, disorganizing the network and the harmonic interactions of the multicellular structure. Due to the high individual energy demand, these cells use a primitive transcriptional program [2]. The tumor organizes a unicellular autonomy to safeguard the survival of the "colony" of malignant cells [3]. The healthy host provides active support to cancer, trying to "heal" the abnormality. Neo-angiogenesis, induced injury current, and numerous other boosts appear, guided by misled general homeostatic regulation of the body.

Cancer starts locally but becomes systemic when the structurally and dynamically disordered tissue appears in the body. The dynamic control is not able to repair the local malignant development due to various reasons: genetic aberration [4], mitochondrial dysfunction [5], and other intra [6] and extracellular [7] hallmarks of cancer. Furthermore, the permanent uncontrolled stress [8], the recognition of the lesion as an unhealed wound [9], the permanent inflammation [10], and the missing apoptotic activity [11] worsen the situation.

Cancer is the disease of the multicellular system disrupting the organized network, exchanging the cooperative advantages to the selfish individual demands [12]. One therapeutic help could support multicellular harmonic control, boosting the standard natural homeostatic regulation for effective action. The task is as complex as life itself, so the external actions are limited. We do not expect any changes from the therapy alone. The intention is only backing the natural control to do the job. Our approach is an electromagnetic action [13]. The fundamental tool for this task is the amplitude-modulated radiofrequency (RF) carrier with $1/f$ spectrum, which supports the homeostatic multicellular harmony, helps to correct the malignant lesion's cellular disorder, and induces apoptosis of the malignant cells. The forcing cooperative harmony may influence the precancerous cells to return to the healthy network. Our objective is to study this possibility considering the personalization of the modulation.

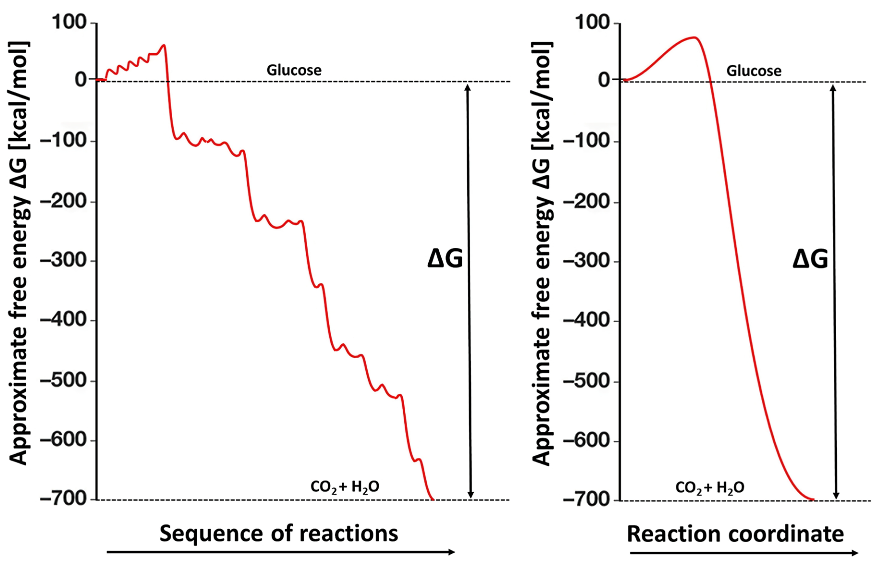
2. Method—The 1/*f* Spectrum

2.1. Embedded Bifurcation Dynamism

The control of life reaction has stochastic feedbacks [14], which drive all the processes in complex, embedded structures. Positive feedback is a process to generate a specific new product or state, with a point of no return. The positive feedback mechanisms are usually complex and have some intermediate potential wells keeping the process controlled and avoiding the expansive quick unregulated outcome. A characteristic example is the catabolism of humans, where the positive feedback is driven with the never-resting electrons: "Life is nothing but an electron looking for a place to rest" [15]. In the metabolism of the eukaryotic cells, the glucose has a degradation, and finally, the process ends in CO_2 + H_2O products, while the liberated energy kept the cells living **Figure 1**.

The positive feedback has no direct general balancing, but the subsequent steps in this have metastable positions, requiring some extra energy to overcome the barriers. The simplest and most common negative feedback regulation processes in a living system have two opposite regulation effects: the promoter and suppressor balance each other. This balancing process compensates for the opposite factors, fluctuating between two possible states **Figure 2**. When the negative feedback is out from the pre-set limits, the process becomes unbalanced, the negative feedback weakens, and a sign of irregularity appears.

The bifurcation potential wells usually have a longer chain of embedded bifurcations as part of the complex process. In this way, the complexity develops a



(a) (b)

Figure 1. The approximate "degradation" of glucose to the final molecules CO_2 + H_2O of catabolism. All peaks are transition states assisted by devoted enzymes, and the wells are metastable intermediate states.

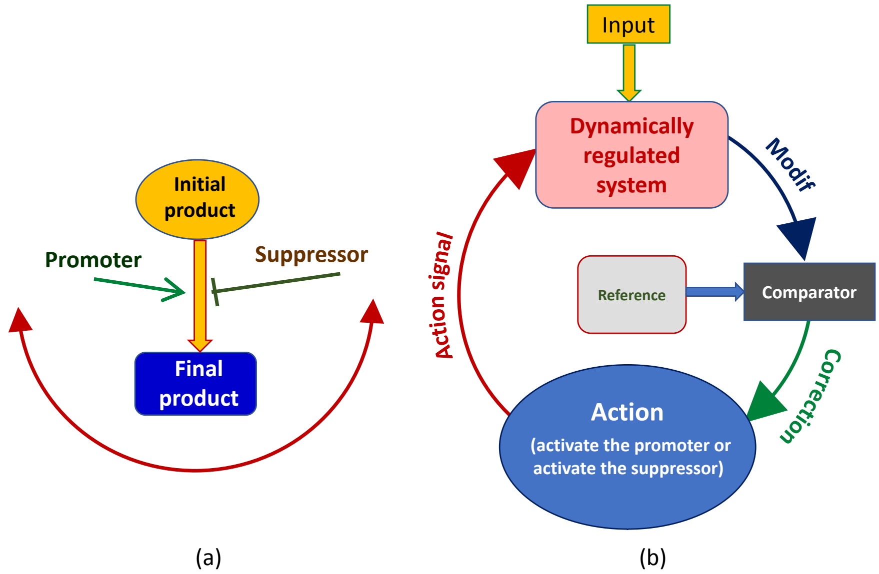


Figure 2. The dynamic balance of the homeostatic negative feedback control. (a) balance of the promoter-suppressor pair (b) the complete circle of the regulation.

multifurcation system at the level of the entire living organism. The primary step of the embedded multifurcation starts with the water structure. The hydrogen bridges allow a chain transport of H^+ ions, creating a fundamental mechanism in living systems [16]. The proton tunneling (jumping) between the water molecules forms low dissipation ionic transport (the proton migrates) [17] [18]. The involved ion multifurcates in the potential wells of the chain connected by the bifurcative hydrogen bridges, connecting the water molecules dynamically. Such construction from bifurcative to multifurcative connection appears in the whole organism following the hydrogen-bridge mechanisms [19] [20] [21]. The bifurcative steps appear in structural connections of the DNA helix connecting the nucleotides, which may cause protein's bending and be involved massively in the stochastic processes of life. Self-organized processes connect the bifurcation steps, which are arranged in fractal structure **Figure 3**.

The amplitudes of the harmonically oscillated particles of the bifurcative potential wells in the self-organized setting form a Cantor set, which is in mathematical expression:

$$x \to f(x) = \frac{\left[\frac{1}{2} - \left|x - \frac{1}{2}\right|\right]}{r} \tag{1}$$

where r is the section removed from the middle of the Cantor's template. The vibration produced by the k-th bifurcation-set (multifurcation) has the following shape

$$x_k(t) = A_k \sin(2\pi f_k t + \varphi_k) \tag{2}$$

The power spectrum of the vibration superimposed on these in the case where f_k is a multiple of f_1 fundamental frequency. The average of x^2 is:

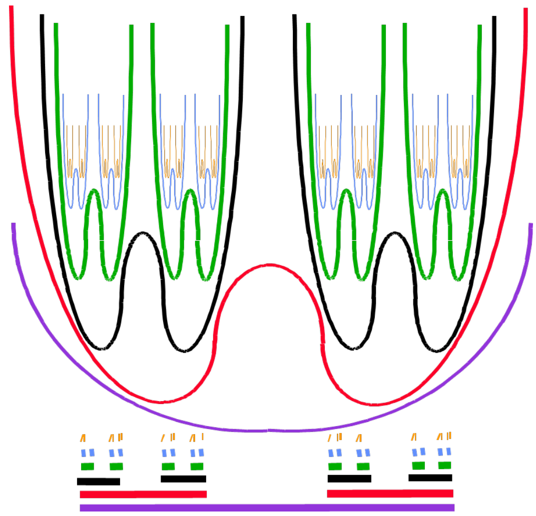


Figure 3. The self-similarity produces the embedded multifunction system. Stochastic resonances promote the bifurcation steps. The probability distribution follows a Cantor-dust fractal.

$$\langle x^2 \rangle = \sum_k \frac{A_k^2}{2} \tag{3}$$

We suppose the expected $1/f$ spectral behavior, so it is a condition of the spectral density $S(f_k) \propto A_k^2$

$$S(f_k) \propto A_k^2 \propto \frac{1}{f_k} \tag{4}$$

Due to the Cantor-set character, using the assumption of (4) when $r = 3$

$$\frac{A_{k+1}}{A_k} = \sqrt{\frac{f_{k+1}}{f_k}} = 3 \tag{5}$$

So the frequencies form a geometric series

$$\frac{f_{k+1}}{f_k} = 3^2 \tag{6}$$

So the k-th frequency

$$f_k = 3^{2k} f_1 \tag{7}$$

This is a discrete power spectrum, but their amplitudes follow the assumed $1/f$ pink noise (4). In the above described discrete subsequent embedding, the particles oscillate in one dimension and are independent from each other. However, the reality differs. The oscillation is three-dimensional. All the directions of the space could be active, and these oscillating dimensions could be dependent. Weak interactions connect the wells, forming networks and dynamical harmony. The net of the weak interactions ensures a stable system with low vulnerability [22]. The natural overlaps create a continuous $1/f$ spectrum, even in this simple model. Self-similarity and self-organization are the general features of the living system, generalizing pink noise in stationary random stochastic processes [23].

The living systems are far from thermodynamical equilibrium, seeking to realize the lowest available energy with the highest efficacy in dynamic stability (homeostasis), balancing the energy incorporation and the energy combustion. The natural processes seek to minimize their energy consumption, using the least-action principle, which drives the biological processes and the biological evolution.

2.2. The Frequency-Order

The living systems show $1/f$ noise in homeostasis, a distribution of the stochastic processes keeping the system in dynamic equilibrium. However, this character does not identify the system because the $1/f$ is a spectrum, a distribution of the frequencies by their power density, without the time series of signals in the organism. The time-dependence vanishes with the Fourier transformation, and the obtained power density gives general information like the status of self-organizing, the scaling, and the dynamic equilibrium of the body; the time-function disappears. Some general info about the interaction chains could be derived from the autocorrelation function, but the actual time-dependent signal remains hidden.

The $1/f$ frequency spectrum is a distribution, which defines various frequencies, taking no attention to their sequences in the actual signal. For example, most musical pieces have near $1/f$ distribution, but they are, of course, very different in their musical sounds. The frequency distribution does not inform us about the temporal sequences of the frequencies. However, the temporal signal is used for modulation, so derive this information from the spectral density function to increase the theranostics approach's efficacy and accuracy. Facing this problem, study first the power spectrum of pink noise, assuming a trivial, energetic criterion for self-similarity. When $f(t)$ is a self-similar function on the whole real axis, we know:

$$f(\tau t) = \tau^k f(t) \tag{8}$$

when the function in (8) is chosen as integrally quadratic:

$$0 < \int_{-\infty}^{\infty} \left| f(t) \right|^2 \mathrm{d}t < \infty \tag{9}$$

The used $\left| f(t) \right|$ is the absolute value of the signal allows complex functions. This is physically a possibility to examine self-similar function pairs. The above criterion for physical signals usually means that the energy of the signal is finite. This is true of all physically meaningful signs [24]. Note the integral of the quadratic function with E:

$$E = \int_{-\infty}^{\infty} \left| f(t) \right|^2 \mathrm{d}t \tag{10}$$

So using (8):

$$\begin{aligned} E &= \tau \int_{-\infty}^{\infty} \left| f(\tau z) \right|^2 \mathrm{d}z \\ &= \tau \left(\tau^k\right)^2 \int_{-\infty}^{\infty} \left| f(z) \right|^2 \mathrm{d}z \\ &= \tau^{1+2k} \int_{-\infty}^{\infty} \left| f(z) \right|^2 \mathrm{d}z \\ &= \tau^{1+2k} E \end{aligned} \tag{11}$$

with substitution of E from (10) to (11):

$$\tau^{1+2k} = 1 \rightarrow k = -\frac{1}{2} \tag{12}$$

Below we prove that Equation (12) leads to the $1/f$ power spectrum. The quadratic integrity (finite energy signals) has a Fourier transform, which is also self-similar in a frequency domain, so:

$$F\left[f(t)\right] = X(j\omega) = \frac{B}{(j\omega)^{1+k}} = \frac{B}{(j\omega)^{\frac{1}{2}}} \tag{13}$$

Taking advantage of this, the Wiener-Khinchin theorem [25] states that

$$\int_{-\infty}^{\infty} \left|f(t)\right|^2 \mathrm{d}x = \int_{-\infty}^{\infty} X(j\omega) X^*(j\omega) \mathrm{d}\omega = \int_{-\infty}^{\infty} \frac{BB^*}{\omega} \mathrm{d}\omega \tag{14}$$

Hence the power spectrum of the self-similar finite energy signal is $1/f$. Note that the signal can also be deterministic, and even as we show below, the theorem does not apply to stationary noises in the above form. In the case of the principle of infinitely long stationary self-similar signals, finite energy cannot be guaranteed. In this case, the physically meaningful claim is the finiteness of the average:

$$0 < \lim_{T\to\infty} \frac{1}{T} \int_{-T/2}^{T/2} \left|f(t)\right|^2 \mathrm{d}t < \infty \tag{15}$$

The repeated above calculation resulting (12), the average power of (15) delivers the same result, namely that the power spectrum of the self-similar signals with finite average power is $1/f$. We have to make some theoretical remarks and move on to ergodic signals and correlation functions to discuss the stochastic processes in the above way. In the case of stationary ergodic signals, the correlation functions can be formed from each representation by forming the following limit value:

$$R(\tau) := \lim_{T\to\infty} \frac{1}{T} \int_{-T/2}^{T/2} f(t) f(t-\tau) \mathrm{d}t \tag{16}$$

Because we assumed finite mean performance, this correlation function exists. Introduce the notation for the T-length representation of the signal. This is defined as:

$$f_T(t) = \begin{cases} f(t) & -\frac{T}{2} \le t \le \frac{T}{2} \\ 0 & \text{otherwise} \end{cases} \tag{17}$$

The Fourier transform of the T-length representation:

$$X(j\omega, T) = \frac{1}{2\pi} \int_{-T/2}^{T/2} f(t) \mathrm{e}^{j\omega t} \mathrm{d}t \tag{18}$$

The average power density of T-length representations approaches the Fourier transformation. Based on this, it might be supposed that every single being's autonomic nervous system produces an individually coded $1/f$ homeostatic noise.

In this sense, we can talk about personalized $1/f$ noise. Transform of the autocorrelation function [26], so

$$\Phi(\omega)=\lim_{T\to\infty}\pi\frac{X(j\omega,T)X^{*}(j\omega,T)}{T}=\frac{1}{2\pi}\int_{-\infty}^{\infty}R(\tau)\mathrm{e}^{-j\omega t}\mathrm{d}t \tag{19}$$

Conversely, the inverse Fourier transform of the average power density is the autocorrelation function, so

$$R(\tau)=\frac{1}{2\pi}\int_{-\infty}^{\infty}\Phi(\omega)\mathrm{e}^{j\omega\tau}\mathrm{d}\omega \tag{20}$$

From this, we obtain the average performance of

$$R(0)=\lim_{T\to\infty}\frac{1}{T}\int_{-T/2}^{T/2}\left(f(t)\right)^{2}\mathrm{d}t=\frac{1}{2\pi}\int_{-\infty}^{\infty}\Phi(\omega)\mathrm{d}\omega \tag{21}$$

expression, which is the Wiener-Khinchin theorem for stochastic signs. As shown above, the Fourier transform of the self-similar signal is a self-similar signal in the frequency domain. With the substitution in (21):

$$\begin{aligned}R(0)&=\frac{1}{2\pi}\int_{-\infty}^{\infty}\Phi(\omega)\mathrm{d}\omega\\&=\tau\frac{1}{2\pi}\int_{-\infty}^{\infty}\Phi(\tau\varpi)\mathrm{d}\varpi\\&=\tau\tau^{\alpha}\frac{1}{2\pi}\int_{-\infty}^{\infty}\Phi(\varpi)\mathrm{d}\varpi\\&=\tau^{\alpha+1}R(0)\end{aligned} \tag{22}$$

According to (11), $R(0)$ is self-similar. The power spectrum $S(\omega)$ equal with $\Phi(\omega)$, as it is shown in (19), which is its definition, so

$$S(\omega)=\Phi(\omega)=\frac{A^{2}}{\omega}=\frac{A}{\sqrt{\omega}}\frac{A^{*}}{\sqrt{\omega}}=\frac{|A|\mathrm{e}^{i\varphi(\omega)}}{\sqrt{\omega}}\frac{|A|\mathrm{e}^{-i\varphi(\omega)}}{\sqrt{\omega}} \tag{23}$$

The power density spectrum is the product of the signal and its conjugate spectrum. Then the temporal representation of the stochastic signal is:

$$f(t)=inverseFourier\left(\frac{|A|\mathrm{e}^{i\varphi(\omega)}}{\sqrt{\omega}}\right) \tag{24}$$

where the phase $\varphi(\omega)$ is an arbitrary function that can be deterministic but can also be random, characterized by its distribution functions. When an ergodic function represents the stochastic process, it facilitates the characterization.

Like it is shown in (24) that each $1/f$ signal differs in the distribution (power spectrum) of a random variable in phase. Since the phase is the carrier of the information, its distribution determines the signal's temporal form, which allows a better understanding of the step-by-step changes of the signal in the biological processes, while the power spectrum gives systemic information.

The scaling of the power density by frequency is a piece of general information about the system. The cancerous lesion is a local disorder that hurts the standard healthy conditions. Consequently, cancer cannot accept harmonic modulation. The signal attacks the cells by absorbing energy, while in the healthy harmonic tissues, these absorptions are much weaker, keeping the harmony in proper rhythm.

It is essential to identify when the system does not work correctly, so have tissues out from the overall self-organized control. The general request of the homeostatic harmony can be forced by a compulsory force by the $1/f$ signal. The following ways could personalize the general harmonization attempt:

1) Apply a $1/f$ random spectrum. This spectrum generates the frequency components randomly, but their distribution is strict. This method well shows the general harmony of the homeostasis, but no information about the actual processes in the molecular reactions of the cells. However, with the relatively high frequency (in the audio range up to 20 kHz, which changes 20.000 times in a second) and the vast number of enzymatic reactions, this method satisfactorily approaches reality stochastic meaning. The reactions occur in a randomized fashion in a large target. There are stochastically several proper excitations from the few billion excited molecular reactions. This is presently the best harmonizing approach.

2) Measure one of the personal electric signals (like heart rate, nerve-activity), and apply it as a compulsory modulator. This approach is very personal, but the signal depends on the patient's actual state, stress, mood, or the development of the disease, so it may be that its power density function deviates from the ideal $1/f$ scaling. In such a case, the modulation is suboptimal.

3) The local physiological signals could detect the target-oriented control signal. This method could compare the harmonic healthy host tissue with the anharmonic malignant tumor. This simple principle, however, has complications:

a) The non-invasive impedance measurement is inaccurate, depends on many internal and external modifying factors, so it is unsatisfactory. If the impedance measurement is not accurate, then why accurate enough treatment with a non-invasive impedance basis? The treatment uses a high-frequency carrier of the modulation, and the radiofrequency delivers the information to the target, and the electrical nonlinearity of the cellular membrane applies the info directly to the targeted cells.

b) Choosing the control target is not easy in such a complex disease as malignancy, where we have no precise information about the systemic effect of the tumor. (The present imaging and measuring technique or not cellular accurate.)

c) An electric signal is requested directly from the control target to measure its physiological harmony. This is usually the local arterial blood-flow fluctuation. In most cases, it needs invasive measurements, and even with this, the accuracy to form an appropriate signal is low.

4) The modulation signal may be applied not only for the treated target but also for the central energy supply manifested in the heart rate. The heard delivers the oxygen, nutrients, and electrolyte components (including special cells and compounds) which energize the dynamics all over the body. The heart-rate

variation is the result of the parasympathetic and sympathetic controller signal summary in the sinus nodes [27]. The $1/f$ signal of the vagus nerve could harmonize the overall metabolism by nerves' action and control the oxygen supply by the heart rate, which determines the homeostatic stochastic process.

3. Result—The Personalization

The template will number citations consecutively within brackets [1]. The sentence punctuation follows.

The study of biomarkers evaluates the actual status of the organism with possible indications of the presence of locally systemically derail of homeostasis, forming pathological condition [28]. A particular group of biomarkers is the tumor markers, which refers to an elevated amount of body-identical substance in a tumorous patient, while it has only a low amount or not at all in a non-tumor patient. The tumor markers do not have enough diagnostic value in prevention, so the biomarkers have emerging importance indicating deviation from the healthy homeostatic balance. The deviation of the biomarkers from the healthy standard has three values [29], which are especially important for cancer [30].

1) Diagnostic biomarkers help the accurate analysis [31], and the design of clinical trials [32];

2) The prognostic biomarkers can indicate the possible prognosis of the disease [33];

3) The predictive markers can inform about the efficacy of the applied therapy [34].

The medicine practice needs reliable biomarkers indicating a disease/tumor early, showing its growth, spreading, being effective, or ineffective in therapy. It is extremely important to assess and monitor the general condition of patients during treatment to assess how well they are receiving the therapy they are receiving, but we can also obtain the information needed to maintain an adequate quality of life. The Karnofsky scale (in the range of 0 to 100, the patient's state of health), the ECOG system (scale of 0 to 5) may be helpful. In addition, questionnaires assessing physical, social, emotional, and functional well-being, such as EORTC QLQ-C30 or FACT-G [35].

According to the present practice, sampling is necessary to determine the prognosis of the cancerous patient. The pathologist provides staging and grading based on the standardized categories. The basic guidelines and protocols describe a generalized proposal for treating patients considering the pathological results. However, the prognostic factors used at present lack stable reliability [36]. Although it would be desired to provide personalized prognosis and decision-making, taking into account the patient's individual clinicopathological and psychological status. Any new reliable prognostic factor and connected therapies (theranostic methods) are expected to step towards personalized treatment. According to the principal considerations [13] [14], and the emerging practices [37], the modulation of a carrier signal could be a reliable option of personalized therapy. The application of modulated carrier presently applied mostly on oncology, but its non-oncological applications are also possible [38] [39] [40] [41].

3.1. Systemic Regulation

The homeostatic regulation shows some measurable electric signals for non-invasive detection of its proper functioning. The non-invasive detection of biomarkers has an extra advantage: less burdensome for the patient and more straightforward for the physician. This practical request emerges the various electromagnetic signal detection, like the Electroencephalogram, (EEG); Electrocardiogram, (ECG); Electromyogram, (EMG); Electrooculogram, (EOG); Electroretinogram, (ERG); Electrogastrogram, (EGG); Galvanic skin response, (GSR); electrodermal activity, (EDA), electrical impedance tomography (EIT), etc. These signals have not only prognostic and diagnostic value, but could be active therapeutic option to correct the deviations [42] [43] [44] [45]. In the following, we study two undoubtfully systemic regulatory signals: the heart rate and the nervous activity.

3.1.1. Vagus Nerve Signal

There are several methods for studying the autonomic nervous system. There are studies based on cardiovascular reflexes elicited by provocative maneuvers. Neurotransmitter levels can also be examined. The cholinergic part of the autonomic nervous system can be performed, for example, by examining sudomotor function (the reaction of sweat glands to various stimuli) [46].

The vagus nerve has an important homeostatic role. Its efferent position gives regulation signals for many muscles and various organs. It participates in the cardiovascular, respiratory, gastrointestinal, metabolic, control, and glucose homeostasis (pancreas, liver, kidney) regulation and controls inflammation by the spleen [47]. The afferent activity includes a significant part (>80%) of the nervous structure transmitting information to the central nervous system about the functioning of the organs of the body [48].

Several studies proved the therapeutic effect of vagus nerve stimulation (VNS) [49]. The emerging application of VNS is transcutaneous, primarily focusing on the auricular branch of the vagus nerve [50]. This non-invasive method targets several disorders, like migraine, tinnitus, headache, pain, applied in both cervical and ear sides. Importantly intensive studies started to clear the possible application of the VNS autoimmune and autoinflammatory diseases [51] and immunity [47].

The importance of studying the autonomic nervous system, among other sciences, is already outlined in oncology. Autonomic neuronal dysfunction has been shown to affect 80% of patients with advanced cancer [52]. The vagus nerve controls glucose homeostasis [53], which is particularly important for cancerous processes. Vagus nerve activity affects tumor growth by inhibiting tumor-promoting mechanisms. The significance of its study in a wide variety of tumors is known. The results of several articles show that vagus activity may play a prognostic role in cancer.

Tumor cells can take advantage of the benefits provided by factors secreted by nerve fibers to produce a stimulating microenvironment for the survival and proliferation of their cells. A reciprocal interaction exists between tumor cells and nerves in humans [54]. Tumor cells induce nerve growth in the tumor microenvironment by secreting neurotrophic factors. The nerves show up as essential regulators of tumor progression. Sympathetic nerves drive tumor angiogenesis with noradrenaline release, increases the migration capacity of tumor cells, and determines the direction and development of metastases, while the cholinergic fibers of the parasympathetic nervous system, in turn, infiltrate tumor tissue and affect tumor cell invasion, migration, and distant metastases [55]. The sensory and parasympathetic nerves stimulate tumor stem cells, while at the same time, the parasympathetic nerves tend to inhibit tumor progression. This balance forms the dynamic complexity of the nervous interactions [56].

The vagus has been an essential pathway in the early preclinical stage of tumorigenesis through the information to the brain about preclinical tumors with an immune-nerve information transformation. It partially regulates tumor formation and progression [57].

The tumor microenvironment has a fundamental influence on its features [58]. It contains innate and adaptive immune cells [59], which have Janus-face behavior, could inhibit [60] or support tumorous processes [61]. A clinical trial shows the feasibility of vagal neuroimmunomodulation as the prognostic factor for pancreatic cancer, and so, the method offers a new prognostic biomarker of advanced cancers [62]. Furthermore, active adjuvant therapy of neuromodulation of cancers improves the quality of life in advanced cases [63]. It is clinically shown that the VNS increases the complexity of heart-rate variability, allowing more stable homeostatic control [64], having a higher probability of a better quality of life and more prolonged survival.

The experimental and clinical observations indicate that one of the most promising and far more objective methods for studying the autonomic nervous system is to analyze heart rate variability (HRV).

3.1.2. Heart Rate Signal

It was a long time ago realized that the chaos in physiology has special meaning [65]. The "constrained randomness" [66] is usual in physiology, and its study is a valuable tool to understand its mechanisms as well as recognize the deviation from "normal". The analysis of the noise-like profile of hear-beat in the healthy subject shows $1/f$ power-law distribution was recognized early [67], and this "chaos" was associated with time-fractal processes in the living organisms. The heart frequency components' expected flat or normal distribution became long-tail, self-similar distribution with scaling possibility.

The heart rate variability (HRV) describes the variability in the intervals between heartbeats. The temporal fluctuation of heart rate is due to autonomic nervous system regulation; it is created by interacting the sympathetic and parasympathetic nervous systems contributing to the measured variation of the signals [68]. HRV strongly correlates with vagus activity [69]. The most common area of HRV analysis is the study of cardiological problems [70]. However, it is often used for other diseases, like diabetes [71], renal failure [72], neurological [73], and psychiatric changes [74], but it is also used for sleep disorders [75] and some psychological phenomena [76]. The viability of using HRV measurement is based on non-invasiveness, ease of construction, and reproducibility [77]. Nowadays, the HRV offers a possible prediction of disease onset and prognosis [78], and so, its application has a significant increase in oncology [79].

The change in heart rate from beat to beat (RR [ms] intervals, the most observable peak in QRS complex in ECG signals) results from the balancing interaction of parasympathetic and sympathetic effects on the sinus node [80]. The RR is frequently estimated by heart rate (HR [beat/min]), which is easy to measure in daily practices. The variability is most frequently measured by time-domain analysis. The basic parameters to evaluate its uses the n^{th} RR interval ($(\mathrm{RR})_n$), and the average value ($\langle \mathrm{RR} \rangle = \frac{1}{N}\sum_{n=1}^{N}(\mathrm{RR})_n$). The calculated time-domain evaluation parameters are:

- the standard deviation of RR ($\mathrm{SDNN}[\mathrm{ms}] = \sqrt{\frac{1}{N-1}\sum_{n=1}^{N}\left[(\mathrm{RR})_n - \langle \mathrm{RR} \rangle\right]^2}$)
- the square-root differences between the successive RR intervals: ($\mathrm{RMSSD}[\mathrm{ms}] = \sqrt{\frac{1}{N-1}\sum_{n=1}^{N-1}\left[(\mathrm{RR})_{n+1} - (\mathrm{RR})_n\right]^2}$).

Some other characterization of the time domain of HRV is used for particular purposes, like

- NNxx [beats], is the number of successive RR interval pairs that differ more than xx [ms];
- pNNxx [%] is the NNxx divided by the total number of RR intervals.

The time-domain of HRV changes is analyzed for its short-range (SD1), which is connected to the RMSSD [81] and long-range (SD2) features [82]. The Poincare plot is an excellent visualization of the short and long-range changes by studying the subsequent RR-intervals; plots each RR_{n+1} as a function of the previous RR_n interval [83]. Poincare plot analysis gives info about long-range by the $\mathrm{RR}_{n+1} = \mathrm{RR}_n$ line visualizing how continuous the development in step-by-step points, while its perpendicular line in the midpoint (zero points) shows how the short-range deviates from the long trends, compared the beat-to-beat info to the expectation of the longer performance of the heart [84]. The nonlinear homeostatic regulation could be followed by Poincare sections [85], with "stroboscopic flashes" synchronized to the neuron activity. Due to its simplicity and clearness, an emerging quantitative-visual technique categorizes the degree of heart failure by functional classes in patients [86]. The SD1 and SD2 can be calculated with standard time-domain parameters [87]. The calculation needs to introduce the standard deviation of the successive differences of the RR intervals, denoted by $\mathrm{SDSD}=\sqrt{\left\langle\left(\Delta \mathrm{RR}_n\right)^2\right\rangle-\left\langle\Delta \mathrm{RR}_n\right\rangle^2}$, where the $\langle\ \rangle$ a sign denotes the mean (average) value, and so $\left\langle\Delta \mathrm{RR}_n\right\rangle=\left\langle\mathrm{RR}_n\right\rangle-\left\langle\mathrm{RR}_{n+1}\right\rangle$. The short and long-range characteristic values are: $(\mathrm{SD1})^2=\frac{1}{2}(\mathrm{SDSD})^2$ and $(\mathrm{SD2})^2=2(\mathrm{SDNN})^2-\frac{1}{2}(\mathrm{SDSD})^2$. In stationary conditions: $\left\langle\Delta \mathrm{RR}_n\right\rangle=\left\langle\mathrm{RR}_n\right\rangle-\left\langle\mathrm{RR}_{n+1}\right\rangle=0$. In this case, we get statistically: RMSSD = SDSD. In consequence, RMSSD has a role in both the short- and long-range interactions in stationary conditions. Naturally, the HRV results and parameters depend on the time length of the registration [88].

The detrended fluctuation analysis (DFA) method is devoted to the scaling of correlation inside the time-domain of the signal [89]. This particular method scales the slopes (trends) of the linear regression fit to the *n*-length grouped segments of measured points in various scales. The sum of actual deviation of the points in the group from their average value is: $y(k)=\sum_{j=1}^{k}\left(\mathrm{RR}_j-\langle\mathrm{RR}\rangle\right)$. Fit a linear regression (least-squares method) to these points. The obtained regression line is $y_n(k)$, and so the detrended series $F(n)$ is scaled by *n*: $F(n)=\sqrt{\frac{1}{N}\sum_{k=1}^{N}\left[y(k)-y_n(k)\right]^2}$, calculating it with different segments and shown in double logarithmic scale vs. *n*, [90] **Figure 4**. The categorization of the noises is similar to the power density, but the DFA slopes differ from the power density slopes.

The relation of the SDNN and the DFA shows a connection to predicting the survival of patients studying in 7 years intervals [91]. When both parameters (SDNN and DFA) are high, all patients survived 7.5 years. When both were low, 50% of the patients involved in the study died within 2 years. In the groups with high DFA and low SDNN 60% died under 2.5 years, while the SDNN was high and, DFA low, 70% died within 3.5 years. Results support the idea that the health status needs high self-organizing in the system. When the self-organized chaos starts to disappear, and a series of subharmonic bifurcations appear, the ventricular fibrillation becomes more likely [92] [93], the bifurcation phenomena are pathological [94]. Note, the bifurcation in this meaning decreases the self-similar time-fractality, which appears again when the bifurcative processes are sequentially inserted into each other (fractal process) and form Cantor-like fractal in the dynamics, shown in **Figure 3**.

The variation evaluation with time-domain has some problems because the form of the signal could substantially differ while the RR average and the RR standard deviation could be identical [95]. The frequency domain, determining the $S(f)$ power density, gives information about the distribution of the frequency components, so it clears the form of the signal [96]. The spectral analysis is a valuable tool in the analysis of the autonomic function of HRV [97]. The study of the frequency spectra reveals the healthy dynamics of the heart and is related to the overall homeostatic condition.

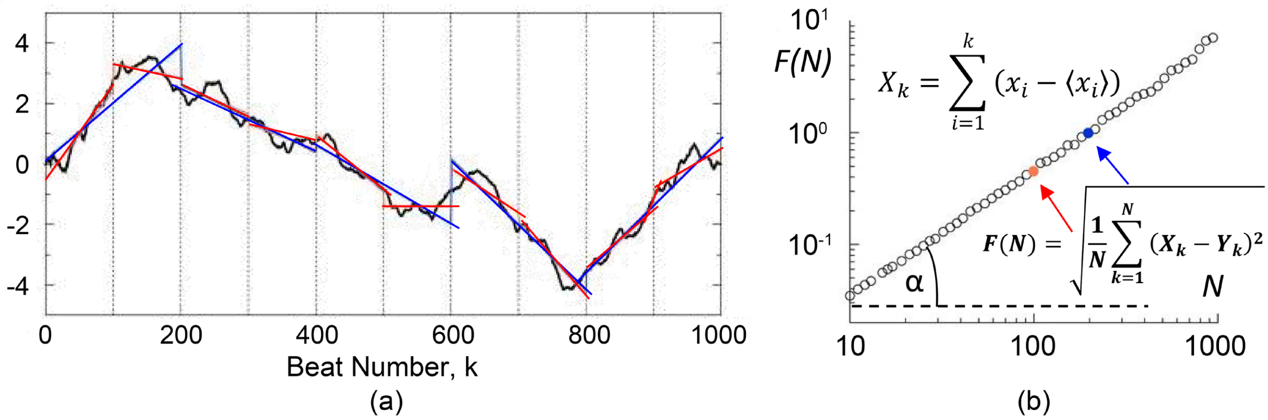


Figure 4. The detrended fluctuation analysis (DFA) method [90]. (a) The process of evaluation of scaled groups of noise parts by the linear regression model. Red lines are the best fit for the subsequent intervals counting 100 beats. The blue fits 200 beats and so on with all possible groups of the beats. (b) The measured slopes from (a). The points for red and blue fits are indicated on the line. The scaling clearly shows linear dependence of grouped slopes.

The frequency domains divided by the physiological ranges [98] like:

- Power ($S_{ULF}(f)$[ms^2]) ultra-low frequency range (≤0.003 Hz) power density ($S_{ULF}(f)$[ms^2]), follows the change s of the body's core temperature, the circadian rhythm, the renin-angiotensin controlling system, and the metabolic processes;
- Power ($S_{VLF}(f)$[ms^2]) of the very-low-frequency range (0.0033 - 0.004 Hz) observes the long-range controlling mechanisms, hormonal processes, heat-control;
- Peak frequency ($P_{LF}(f)$[Hz]) in the low-frequency range (0.004 - 0.15 Hz) is connected to the baroreflex activity and the balancing of sympathetic and parasympathetic nerve actions;
- Power ($S_{LF}(f)$[ms^2]) in the low-frequency range (0.004 - 0.15 Hz) is connected to the baroreflex activity and breathing;
- Peak frequency ($P_{HF}(f)$[Hz]) in the high-frequency range related to vagus nerve tone;
  - for adults (0.15 - 0.40 Hz);
  - for babies (and sometimes after sports activity) (0.24 - 1.04 Hz);
- Power ($S_{LF}(f)$[ms^2]) in the high-frequency range related to vagus nerve tone (0.15 - 0.40 Hz);
- Sometimes the ratio of the power of low (0.004 - 0.15 Hz) and high (0.15 - 0.40 Hz) frequency bands ($\frac{S_{LF}(f)}{S_{HF}(f)}[\%]$) is used to study the balance of the vagal and sympathetic activity.

Through the connections of the autonomic nervous system, vegetative, somatic, and psychic effects are integrated into the instantaneous heart rate and variability [99]. Due to the neuro-controlled (sympathovagal) balancing, the HRV is a feasible parameter to quantify homeostasis [100]. In consequence of the homeostatic character, its measurement could be a valuable tool in clinical practices [101].

The vagus-mediated HRV may be associated with higher-level (brain) executive functions. One region, the anterior cingulate cortex, was interestingly found to be associated with both vagus activity and cellular (NK-cell) antitumor immunity [102].

Inflammatory markers and HRV parameters show correlation. The LF-HRV was inversely proportional to CRP, IL-6, fibrinogen, and HF-HRV was inversely proportional to CRP and fibrinogen. These also supported the existence of the vagal anti-inflammatory pathway [102] [103].

Vagus tone (measured by HRV) influences the nervous-immune response to acute stress. This was demonstrated in a study in which people with low and high baseline HRV participated and were presented with a learning task (acute stress factor). With this acute stress, NK-cell and noradrenaline levels in peripheral blood changed only in the high HRV group. Both prefrontal cortex and striatum activity correlated only with values indicative of the immune system only in the high HRV group. It is hypothesized that high vagus tone may mean a more flexible top-down (brain) -down (immune system) regulation [104].

The frequency domain is a helpful tool for analyzing the signal components, but the obtained frequency distribution does not inform us about the signal trends and how the segments correlate. For the personalization, the amplitude-phase has to be considered, as shown in (24).

The HRV can be a valuable biomarker to assess disease progression and outcome, and even it could be the future remote, wearable biomarker technology [99], which controls not only the diseases, b but also nutrition and wellness [104].

The HRV contains the homeostatic stage of the patient, so it mirrors the various, not disease-connected parameters (like the age, gender, medications, physical and mental status, and even such simple parameters as the body-position, respiratory rhythm, stress) [105]. This sensitivity of general conditions could influence the medical decisions, which develops a distrust in the method. High practical routine and well-controlled conditions are necessary to obtain the medical value of the results. Furthermore, HRV does not directly measure parasympathetic or sympathetic activity. Its features are indirect, only qualitative information on the autonomic activity, the quantitative measures need independent methods. In addition to methodological errors, there may also be technical pitfalls in data collection, signal processing, and interpretation, leading to inaccurate HRV measurement, l and wrong medical decisions [106] [107]. The mixed information causes that the HRV application as a diagnostic tool does not widely apply in medical practice.

3.2. Local Effects

The modulation is well applied locally in the tumor treatment [108] by forcing the local arrangement order in space-time to fit homeostasis. The local application has similar goals that the systemic VNS, forcing the healthy balance. However, the local application is only in the small part act on the nervous system (mainly on parasympathetic, while the selection is connected to the function of the vagus). The dominant effect forces the healthy local arrangement in space (intercellular bonds) and in time (intracellular signal-transmissions). The practice of local application is the modulated electrohyperthermia (mEHT, trade name: oncothermia®), which is widely applied in clinical practice [109].

3.2.1. Pattern and Molecular Recognition

The differences between the tumor and healthy host tissue are significant. The tumor cells have a higher metabolic rate than the host because of proliferative energy demand, have no networking connection with the neighboring cells, separate individually, have different membrane structures with more transmembrane lipid rafts, and differ in their overall structure too. This last is used by the pathologist when studying the pattern of the specimens and recognizing the pattern deviation from the expected healthy order. This pattern recognition is one of the factors of the diagnosis, staging, and prognosis too. So, the tumor structure differs, which can be recognized by the homeostatic signal, due to the missing dynamic harmony. In this way, the disordered tumor selectively absorbs energy from the harmonic fluctuation (modulation with $1/f$ noise), and the various consequences kill the cells. The free genetic information allows recognizing the deviation by the adaptive immune system, which may act against [110] [111].

A part of the modulation effect is the broken cadherin complexes' re-bonding and allowing the intercellular connections again [112] [113]. This reconstruction turns the individual precancerous cells to the network and blocks their movement, decreasing the risk of metastases. The rebuild network allows the intercellular connections, gives the cell a chance to return to normal conditions, or has a signal, and turns to apoptosis.

The physical analysis of temperature-dependent effects of mEHT [114] calculated that the most likely effect is electromagnetic excitation, which develops non-thermal effects of radiofrequency electromagnetic fields [115]. The physical assumptions successfully indicated the possibility that the physical methods may recognize and use the heterogeneity of the target [116]. The vagus nerve assists the body's thermal sensitivity and thermoregulation [117].

3.2.2. Molecular Excitation

Other important local effects of mEHT are the molecular excitations of the cellular receptors and, in general, the transmembrane proteins. The nonthermal membrane's temperature-independent effects of electromagnetic fields had serious debates and controversial opinions. The present research provides some preclinical and clinical data for the nonthermal antiproliferative effects of exposure to mEHT. The excitation promotes membrane vibrations at specific resonance frequencies, which explains some nonthermal membrane effects, and/or resonances causing membrane depolarization, promoting the Ca^{2+} influx [118], or even form a hole on the membrane. mEHT may be tumor-specific owing to cancer-specific ion channels and because, with increasing malignancy, membrane elasticity parameters may differ from that in normal tissues. The Arrhenius plot fits the thermal properties in mEHT experiments [119], so the treatment is a complex mixture of the thermal and nonthermal processes [120]. The protecting chaperones induced by the heat shock are exhausted [121], so the safeguarding does not suppress the electromagnetic reaction. This mechanism resolves the radiotherapy resistance of pancreas adenocarcinoma cells [122].

The molecular excitation is proven in vitro, showing how different the mEHT complex electromagnetic therapy is from conventional heat-therapies [112]. The recent review of the tumor-damage mechanisms collects the preclinical results [113].

4. Discussion

The modulation of the external bioelectromagnetic signals has well-explained principles [13]. The carrier frequency helps in the selection mechanisms, while its modulation acts. The modulation supports homeostasis by its time fractal ($1/f$) frequency distribution [108]. The modulation could have multiple effects locally and systematically. The local force for the homeostatic control acts as a further selection factor regarding the lost control of the tumorous cells. Furthermore, the modulation forces the healthy dynamical order providing a compulsory process for apoptosis of the out-of-control cells. HRV may characterize the homeostasis [124], presenting the complexity of the system.

The well applied time-fractal current flow may activate the structural fractals in the living systems, and the personal fractal structure could modify the time-fractal pattern, too [125]. The fundamentally non-linear physiological system dynamics work on the edge of chaos, a border of order and disorder showing a constant dynamic interplay between these states [126]. The challenge of the homeostatic equilibrium is the apparent chaos. The chaos looks complete randomness which is only ostensible. The chaos in biosystems results from the stochastic self-organizing and the energetically open system, which directly and permanently interacts with the environment. Its structural and temporal structure is fractal, which appears in the fundamental arrangements of the self-similar building and dynamism of the energy exchanges internally and externally. The living processes are complex. They are in self-organized criticality (SOC) [127], which is formulated, as the "life at the edge of chaos" [128]. This chaos is the realization of a well-organized stochastic (probabilistic) system [129]. The disordered chaos is apparent [130].

A simple bifurcation could help to understand this "edge of the chaos" phenomenon. The processes must keep their dynamic energized form. When their energy at the energy breaking point is too low, the process stops and "freeze" in one of the potential wells. However, when the provided energy is too high, the system loses its control, the promoter-suppressor balance can't regulate the processes **Figure 5**. (Like Einstein formulated: "Life is riding a bicycle. To keep your balance, you must keep moving." [131]) The common idea that bio-systems evolve toward equilibrium is a misperception of reality.

Self-organized chaos was studied in all the living processes like, for example, in immune activities [132], in nerve system [133], in genetic phenomena [134]. The realization of the "edge of chaos" is very personal due to the determining parameters, and their intensity differs from person to person [135]. This character of the living complexity requests personalized treatments.

DFA evaluation of the signal measures the self-similarity scaling of the fluctuations by scaling parameter. This evaluation is similar to the box methods in structural evaluation of the fractals when the scaling is the size of the box like in DFA, the size of the scaling interval. The other time-domain studies focus on the standard deviations of the fluctuations (like the HRV methods the SDNN), which also depends on the length of the investigated interval so also has similarities with boxing evaluations. The standard deviation changes by the s box-sizes in the N_s step-number, and has a scaling behavior:

$$S(s) = \sqrt{\frac{1}{N_s}\sum_{i=1}^{N_s}\left(x_i - \langle x_i \rangle\right)^2} \propto s^H \tag{25}$$

The exponent is named in honor of HE. Hurst, who first observed this scaling at the water level fluctuations at the Aswan dam in Egypt. The Hurst exponent, H characterizes the scaling exponent of the $S(f) = f^{-\beta}$ power density function (PDF, frequency domain) fitted to the scaling function (calculated for $q = 2$) in the time domain:

$$\beta = \begin{cases} 2H - 1 \text{ if } -1 < \beta < 1 \text{ (PDF)} \\ 2H + 1 \text{ if } +1 < \beta < 3 \text{ (PDF)} \end{cases} \qquad \alpha = H + 1 \text{ (DFA)} \tag{26}$$

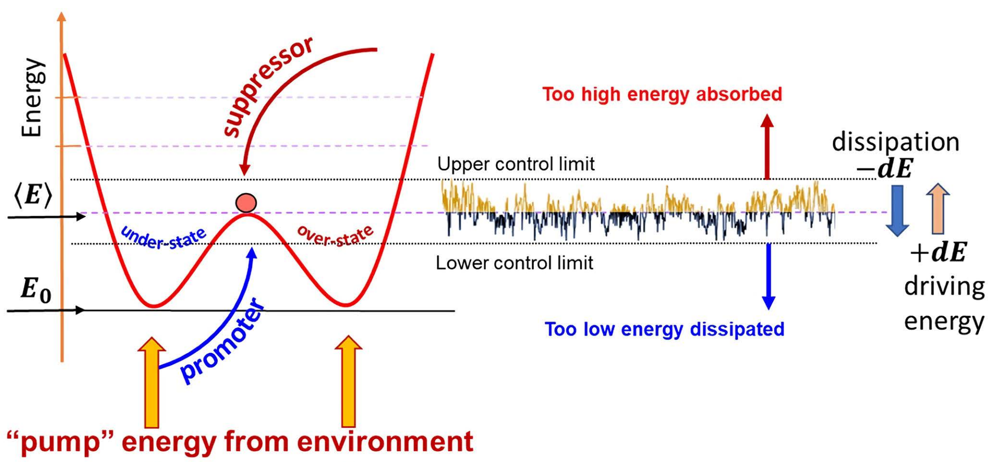


Figure 5. Permanent dynamic changes of the energetically open system cause a never rest situation. The dissipation consumes the energy, while the open, energetic situation drives the process. Promoters and suppressor balance never stop, the dynamism makes life on the "edge of chaos".

In time series: $0 < H < 1$. The $0 < H < 0.5$ describes anticorrelation, while $0.5 < H < 1$ characterizes the correlation, long-memory process. There are two border values: $H = 0.5$ is the while noise (no correlation), $H = 1$ is the pink noise [136].

However, most complex systems have no single scaling. The living body contains variants of fractal templates in space-time, and so the exponents of self-similarity could change by parts. The multifractal analysis considers the scaling as not a global behavior but local (multifractality). The multifractality appears in the dynamics of the biological processes. The scaling varies in time. The nonlinearity of the processes strongly influences the multifractality.

In the case of multifractality since the scaling property is heterogeneous, H will be different for smaller and larger fluctuations in the process and thus the generalized Hurst exponent, $H(q)$ is obtained as a function of q [137]. It is the scaling of the q^{th} momentum of the fluctuation and called generalized Hurst exponent. The generalized scaling function is:

$$S(q,s) = \left(\frac{1}{N_s} \sum_{i=1}^{N_s} \left(x_i - \langle x_i \rangle \right)_s^q \right)^{1/q} \propto s^{H(q)} \tag{27}$$

The generalized multi-scaling gives back the mono-scaling Hurst exponent when $q = 2$ so $S(2,s) \propto s^H$. In the case of monofractality, the scaling property is homogeneous and thus independent of q. With the growth of the "box-size" by growth of s the different variances (scaling functions by q) approaches each other, and at the largest size (the L size of the entire sample) point on a common focus [138] $S(q,L) = SD(L)\ \forall q$, where $SD(L)$ is the standard deviation character of the entire signal.

The fingerprint of the personalized "chaos" is the self-similar noise of interconnected HRV and VNS in both the time (variation-based evaluations) and frequency ($S(f)$ based evaluation) domains. The characteristic behavior of the frequency-based approach is the $1/f$ noise. Consequently, forcing the homeostatic control needs $1/f$ spectrum in the frequency domain. In an ideal case, the frequency domain has a single exponential character. However, it is not the general case; it only approaches a part of the anyway curved double logarithmic plot of the spectral density $S(f)$, which characterizes a multifractal behavior of the system's dynamics.

The multifractal structure changes the frequency by time, so the Fourier transformation, which produces $S(f)$ power density function (PDF) in the monofractal approach, is not constant in all the observed time. The problem of the multifractal analysis has similarity to the Heisenberg principle: one cannot get the infinite time and frequency resolution beyond Heisenberg's limit: $\Delta t \Delta E \geq \frac{h}{4}$ so $\Delta t \Delta f \geq \frac{1}{4}$. Consequently, one can calculate high-frequency resolution accompanied by an insufficient time resolution or has high resolution in time with a poor frequency resolution. The method of wavelet transformation was developed for space-time multifractal description [139].

For proper multifractal analysis, a local power-law had been developed. This method approaches the function with its Taylor series and observes the scaling in the difference of the real and approached function:

$$\left| f(x) - \sum_{k=0}^{N} b_k (x - x_0)^k \right| \le C |x - x_0|^{h(x_0)} \tag{28}$$

The $h(x_0)$ value is the Hölder exponent. This is a local power-law, showing local self-similarity in a given discrete t time-point. In the case of any (multi or mono-fractal) approach $h(t)$ is the power of the scale. In monofractals the exponent is constant: $h(t) = \text{const}$. The Hölder exponent forms trajectories when calculated in real-time. The fractal dimension of disjunct sets of the same Hölder exponents in the histogram approach is the multifractal or singularity spectrum, with generalized dimension $D(h)$, which is mostly used for multifractal characterization. The "size" of the singularity components is $\propto s^{D(h)}$. The monofractal Hurst exponent $H(2)$ tightly connected (but not equivalent) to the maximum (middle) Hölder exponent of the singularity spectra, while the $\Delta H(n)$, the multifractal character described by $\Delta H(n) = H(-n) - H(n)$ is the width of the multifractal spectra. The maximum of $D(h)$ is connected to the autocorrelation and the width of the non-linear character of the processes, introducing the multifractal scale exponent $\tau(q)$ from wavelet transformation [140]. This exponent connects all the multifractal characters:

$$\tau(q) = qH(q) - 1, \quad h(q) = \frac{\mathrm{d}\tau(q)}{\mathrm{d}q}, \quad D(h) = \inf_q qh(q) - \tau(q) \tag{29}$$

The behavior of $\tau(q)$ describes the locally changing dynamic fractals, specifying the details that distinguish these from the global single-exponent character [141], **Figure 6**.

The well-established, widely applied and approved methods of evidence-based medicine (EBM) work with averages in many respects, as the inclusion criteria, like the sub-grouping of the eligible patients by various aspects. The monofractal application fits this approach, representing an overall average of the homeostatic

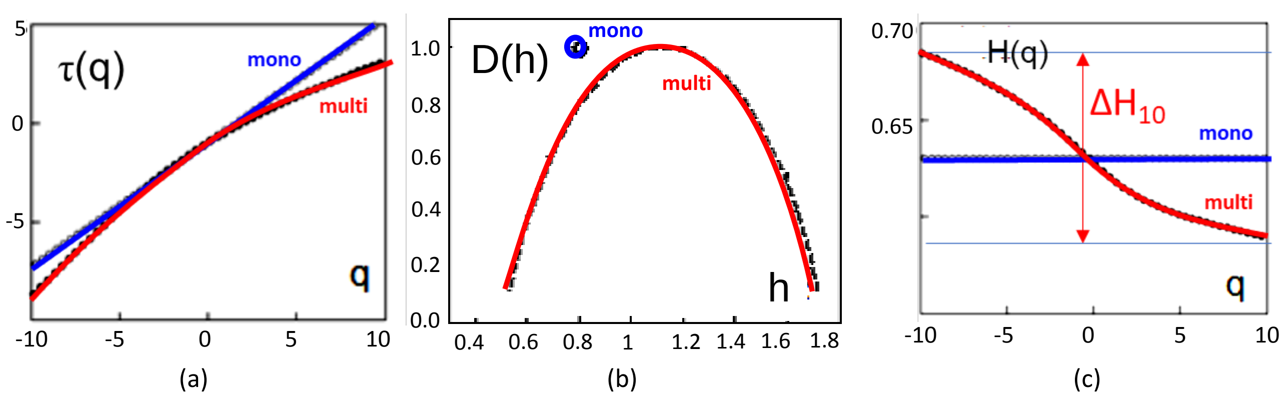
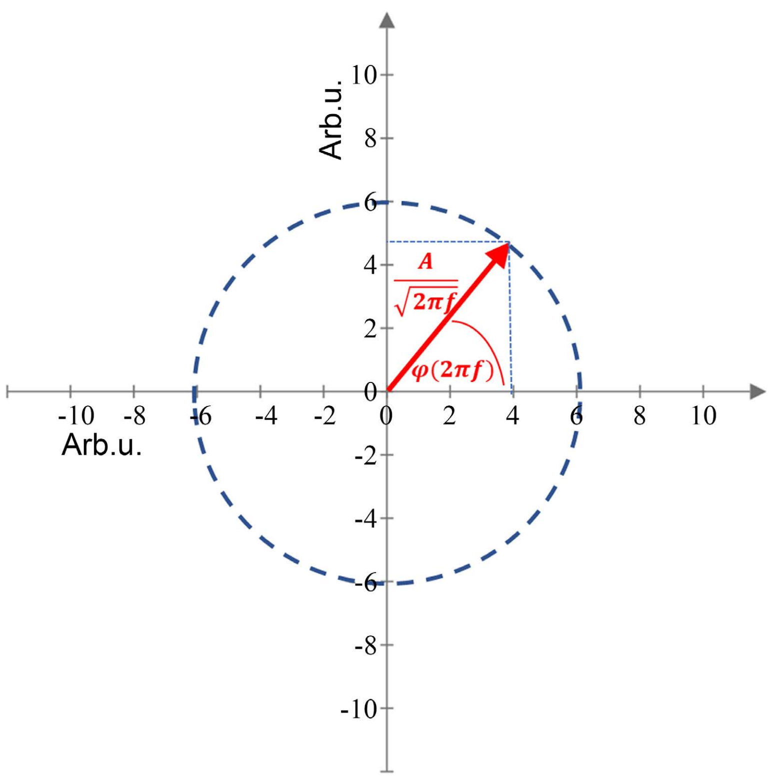


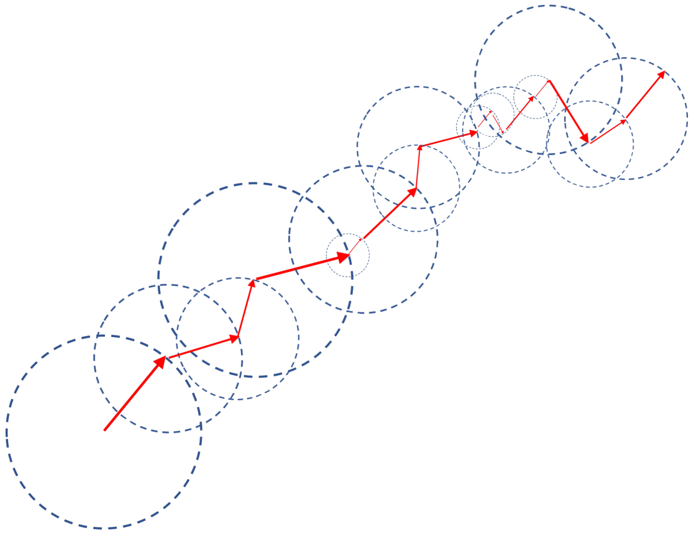
Figure 6. The changes of characteristic scaling exponents in mono-fractal and multifractal stochastic approaches. (a) scaling exponent by q^{th} momentum; (b) multifractal spectrum; (c) the generalized Hurst exponent does not change by $q = H(2)$.

control of the patients. However, the averaging has multiple pitfalls [135] [142]. The primary challenge is the averaging, despite that no such "average patient" who is supposed in the study exists. More personalization is necessary to avoid the averaging errors.

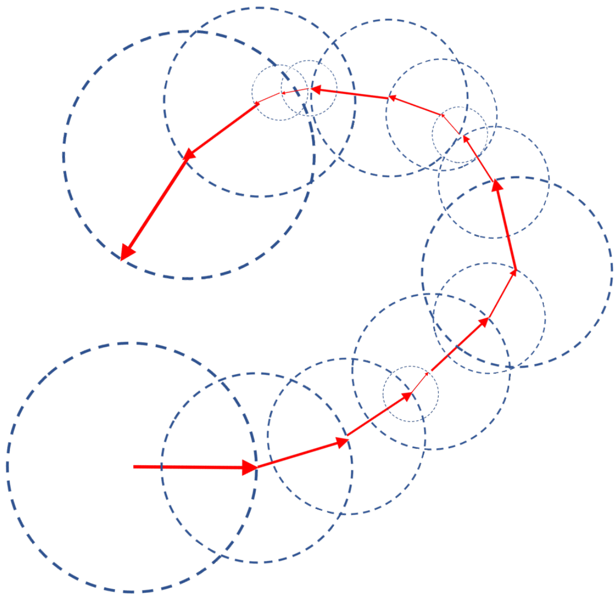
The fine-tuning of the information has to consider the time-domain signal analysis. The personalization principle is the inverse transformation of the time-series from the personally $S(f)$ by the distribution of the amplitude phases ($\varphi(\omega)$) shown in (24). The precise time domain is reconstructed, but it has also averaged in the distribution function of the phase $\varphi(\omega)$. The HRV time-domain has also high averaging due to the form of the signal is not present, only the mean and its standard deviation. However, the HRV and the inverse transformation of the amplitude of $S(f)$ by (24) represent different information about the person, so the combination of the two methods looks the most accurate in our present knowledge. The complex number of the amplitude $A = |A| e^{i\varphi(\omega)} = |A| \left[\cos(\varphi(\omega)) + i \cdot \sin(\varphi(\omega)) \right]$ of $S(f)$ in (24) contains the personal frequency order. The geometric representation of the single term of $S(f)$ in the complex sheet is a circle with the radius $R = |A|$, and a vector with angle of $\varphi(\omega)$. The personal order by geometric description of $\frac{|A| e^{i\varphi(\omega)}}{\sqrt{\omega}}$ from (24) connects these vectors where their size is proportional with $\frac{|A|}{\sqrt{\omega}} = \frac{|A|}{\sqrt{2\pi f}}$ Figure 7.



(a)



(b)



(c)

Figure 7. The series of the $\sqrt{S(f)}$ in personalization. (a) the vector representation of a single component. The vector rotates as the $\varphi(\omega)$ phase angle changes by the changing $S(f)$. (b) an example of the series of $S(f)$s, when the vectors jointly follow each other. The $S(f)$ changes hectically (noisy). (c) another example of the $S(f)$ series with monotonously growing phase angle $\varphi(\omega)$ in a series.

In reality $\varphi(f)$ has a personal distribution, which arranges the frequency order. In a random distribution, we may check the system how we construct the $Si(t)$ time-series of the signal from frequency series with inverse Fourier transformation **Figures 8-10**. Noteworthy that the $S(f)$ function is identical in all reconstruction processes from the $\varphi(f)$ series, because the phase angle does

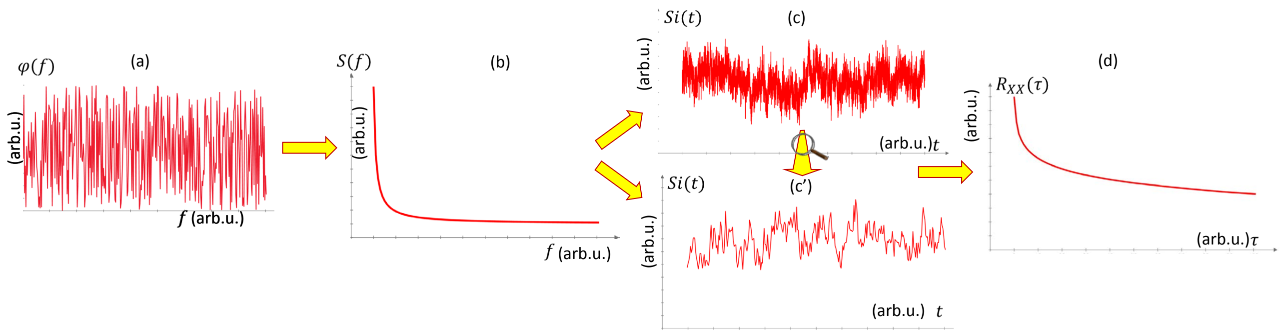


Figure 8. Reconstruction of the time-series from the power density function (PDF) (a) when the $\varphi(\omega)$ phase has a random distribution. (b) The distribution of phase by frequency from the $S(f)$ phase function on the (a). (c) The signal function in time (the time series); (c') the enlargement of the signal function in a small time interval; (d) the correlation function of the $Si(t)$ signal function.

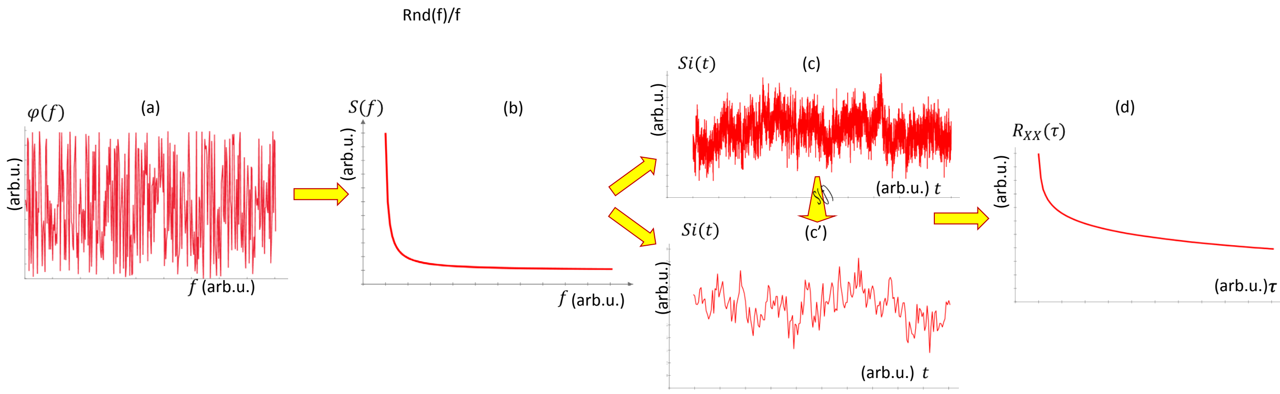


Figure 9. Reconstruction of the time-series from the power density function (PDF) when the $\varphi(\omega)$ phase has $1/f$ distribution. [this figure well follows **Figure 8**; the difference is most obviously seen on the incoming excitation and the $Si(t)$ spectrum] (a) distribution of phase by $1/f$ frequency; (b) the $S(f)$ function from the phase shown in (a) [it is identical with that, repeated only for the control of the calculation]; (c) the signal function in time (the time series); (c') the enlargement of the signal function in a small time-range; (d) the correlation function.

not change the value of the amplitude, only its direction changes on the complex coordination system.

The strong, definite Weibull distribution causes only minimal and mostly regular time series. Probably this is irrealistic in living systems. The periodicity-like form in correlation length is also the consequence of the well-defined original distribution shown in **Figure 10(a)**.

4.1. Forcing Homeostasis by Modulation

The next step of the personalized idea needs to force healthy homeostasis in the patient, who lost it due to the disease. First, the deviation from the healthy state must be measured, which could be checked with the time-(HRV) or frequency-($S(f)$) domain as well. This global information could be the reference for the development of the disease and the chosen treatment's success. Increased risk of progressive disease is connected with the gradual loss of complexity in the decrease

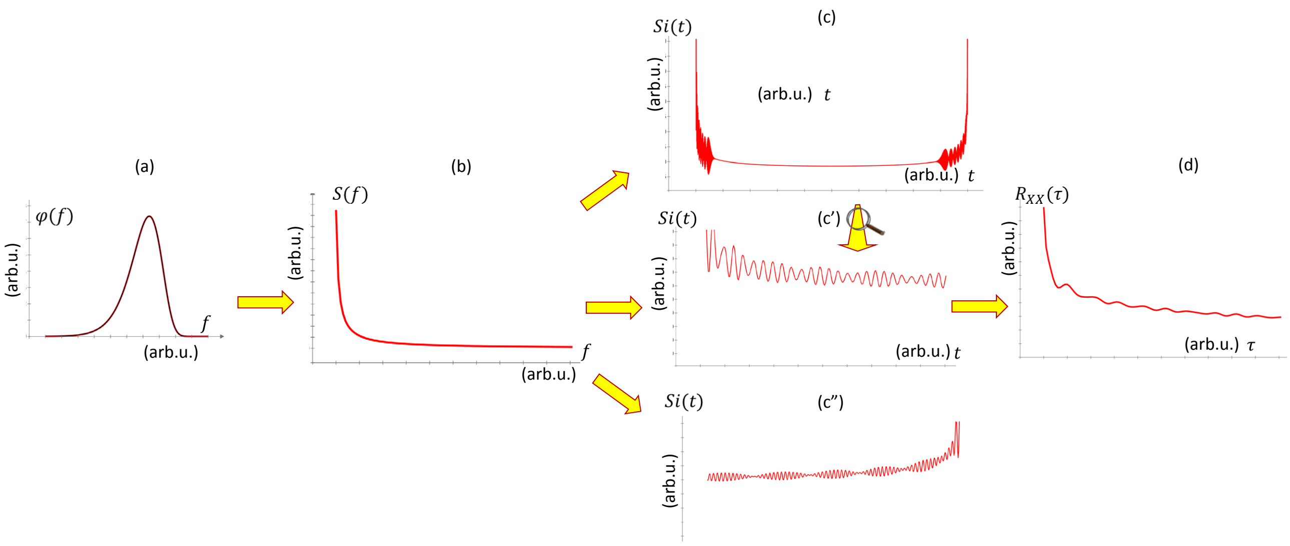


Figure 10. Reconstruction of the time-series from the power density function (PDF) when the $\varphi(\omega)$ phase has Weibull distribution. (a) distribution of phase by frequency; (b) the $S(f)$ function from the phase shown in (a) [it is identical with that, repeated only for the control of the calculation]; (c) the signal function in time (the time series); (c') the enlargement of the signal function in a small time-range; (d) the correlation function.

of the HRV in patients with cardiovascular diseases [64]. It is observed that the VNS associated to the parasympathetic tone, decreases the heart rate accompanied with increased complexity (increased HRV) especially in sleep [64]. The higher HRV values in various bands were positively correlated with disease regression in the actual band category. Higher HRV meant more advanced coping ability and thus better prognosis.

Together with the dynamic equilibrium's general character, it might be supposed that every person has an individual part of homeostatic control. The overall neuronal surveillance by the autonomic nervous system, the immune system, the transport systems, etc., has a particular path specific for a person and produces an individually coded $1/f$ homeostatic noise. In this sense, we can talk about personalized $1/f$ noise. As the (24) shows, the $1/f$ noise spectrum carries many kinds of information which are hidden in the $\varphi(\omega)$ phases of the amplitudes. The phase distribution carries the sequential information of the frequency series.

In the case of one individual subject, the information in the homeostatic noise has the same phase code since these are all results of the work of the same regulatory system. Important perspectives open with the personal homeostatic noise:

- In diagnostics, the measured noise spectrum's irregularities could signal that specific organs do not work correctly.
- In control of the therapy control, the measured changes of the noise spectrum could show the direction of the treatment triggered changes.
- In prognosis, the stored spectrum in individual "noise bank" taken when the patient is healthy could be compared with the actually measured noise prognoses the possible start of the irregularities in the body.

- In therapy, when the healthy fluctuation forces the homeostasis to correct the irregularities and blocks the iatrogenic processes, the healing is actively forced.

The last point is an active function of the noise. We concentrate on this application by personalization forming uniform general $1/f$ signal it is power spectrum. Like all the homeostatic control, the nervous system also follows $1/f$ power spectrum. The general regulator of physiological responses to internal and external stimuli is the nervous system. It is based on two large nervous sets like promoter/suppressor pairs: the sympathetic, which mediates catabolic responses, and the parasympathetic, which regulates anabolic responses. The main component of the parasympathetic nervous system is the vagus nerve. The vagus innervates most tissues dealing with nutrient metabolism, which is crucial for many body functions and cancer development [102] and therapy [58]. The balance of vagus activity with sympathetic regulation needs proper homeostasis [53]. The vagal nerve signals contribute to the care of homeostasis [143] [144].

The homeostatic time-fractal frequency domain (in general, the $1/f^{\alpha}$ noise) is optimal forcing information when no more personal parameters are available This average contains the optimal time-domain fluctuations also when the sole in log-log scale is near to $\alpha \cong 1$. The deviations of $\alpha \gg 1$ mean more step-by-step regulated dynamics (like the brown-movements) while $0 \le \alpha \ll 1$ goes to the white noise direction, to uncorrelated noise.

A possible constraint of proper homeostasis could be an external electromagnetic compulsory signal. The electromagnetic force is an overall effective influence because electromagnetism represents the biologically active force. Choosing the $1/f$ signal is a natural selection to induce a forceful corrective action. The penetration of the electric field into the body depends on the frequency of the signal. The penetration of the high frequencies is shallow, while the low frequencies penetrate deep.

On the other hand, the low frequency does not radiate, so the energy-coupling needs excellent contact in safe voltage application; otherwise, no effect exists. This condition complicates the non-invasive applications. Due to the signal having intensive low-frequency components and the broad spectrum of higher frequencies, the penetration will be heterogeneous; the proper frequency distribution cannot be overcome. The solution could be choosing the higher frequency carrier, which delivers its $1/f$ modulation with approximately proper amplitudes [145]. This modulation solution has a further advantage by its energy delivery, which makes additional mild heating [146], supporting the healthy enzymatic reactions in the body.

A further advantage is that the properly chosen carrier frequency delivers the information to selected regions of the heterogeneous target [147]. Furthermore, the current of the amplitude modulated signal flows through the fractal structures of the living organism, and the necessary frequencies could be selected by the structural dynamism as well. The broad modulation spectrum offers various frequency subgroups, which allows complying with the local demands.

However, it has a disadvantage: demodulation is necessary for the system, which dominantly performs by the cellular membrane nonlinearity [14]. The modulation keeps the system in the regulatory interval, helps the complex living processes correct the faulty regions, and re-establish the healthy control [148] [149].

4.2. Immune Effect of Forcing Homeostasis

One of the effective systemic regulators of homeostatic controls is the immune system. Immune-system terminates many diseases and helps balance the symbiotic life with biotas and broader meaning, as the fundamental cellular reaction, control some inter and extracellular events by molecular chaperone functions [150] [151].

Research on the neural control of the immune response has traditionally focused on the role of the sympathetic nervous system and sensory nerves. However, recent studies have highlighted the role of the efferent parasympathetic system, particularly the vagus nerve, in immunomodulatory actions [58] [152]. The nervous and immune systems communicate in two-way pathways to limit inflammation and maintain homeostasis [58]. The vagus nerve stimulation activates neuroimmune reactions [153].

The vagus nerve is one of the modulating components of innate (like NK-cells) and adaptive (like T-cells) immunity [58]:

- inhibits the TGF-β1, which increases NK-cell expression;
- supports the expression and activity of cytotoxic T-lymphocytes;
- down-regulates the helper T-cells ($CD4^+$ function).

Efferent hepatic vagus activity has anti-inflammatory effects through local IL-1β and IL-6 secretion. This may be an important part of the theory of the beneficial outcome of the relationship between vagus and tumors [154].

The vagal activity reduces the inflammatory response by reducing cytokine release [103]. The B, and C fiber subtypes of the vagal nerve are involved in regulating the heartbeat [103]. This neuroanatomy suggests that the regulation of heart and inflammation by the efferent vagus can be separated. Electrical stimulation (1 V, 5 Hz, 2 ms) was found to be sufficient to elicit an anti-inflammatory effect but did not affect heart rate. Higher striding results decrease in heart rate; consequently, the vagal A fibers are connected to the anti-inflammatory signals. This separation limits the correlation between HRV and vagus-mediated anti-inflammatory effects [103].

The vagal immunomodulatory effect (cholinergic anti-inflammatory pathway) is intertwined with acetylcholine activity. Various immune cells (lymphocytes, macrophages, mast cells, dendritic cells, and bone marrow lymphoid and myeloid cells) express the significant components of cholinergic systems (acetylcholinesterase, choline transporters, AchE, nAChR) and produce acetylcholine. Consequently, the cholinergic system may play a role in regulating the immune response through immune cells [58].

Other systemic effects of vagus nerve stimulation were observed in better outcomes in conditions such as irritable bowel syndrome, metabolic syndrome, diabetes, sepsis, pancreatitis, depression, pain, and epilepsy [102]. Low vagus nerve activity correlates with worse outcomes [102].

An important observation of the modulated treatment is the immunogenic hyperthermic action [155], which can be improved by the independent stimuli of the immune system by dendritic cell therapy [156] [157], or viral therapy [158].

4.3. Cancer and Homeostasis

Tumor cells and the connective tissue surrounding them contain immune cells. However, these cells are double-edged weapons; they can inhibit but also promote tumor growth. The inhibition processes are:

1) activated lymphoid cells can control the tumor growth and malignancy;

2) dense infiltration of T lymphocytes correlates with better prognosis.

While there are promoters:

- tumors often break down the tumor-infiltrating lymphocyte activity;
- supports the differentiation of tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), promote tumor growth by secretion of growth factors, and inhibition of T lymphocytes.

Mediators and cellular implementers of inflammation are essential components of the local environment of tumors. In some tumor types, inflammatory conditions are already present before malignant transformation occurs. Inflammation promotes proliferation, survival of malignant cells, angiogenesis, metastasis, weakens the adaptive immune response, alters the response to hormones and chemotherapeutic agents. The molecular mechanism of this tumor-associated inflammation may be an important therapeutic and diagnostic target [1]. In some types of tumors, oncogenic transformation induces an inflammatory microenvironment that promotes tumor development [159]. The stimulated vagal activity suppresses the inflammatory developments [58]. Most articles examining the relationship between HRV and tumor prognosis consider vagus activity to be systemic as a positive effect. Analysis of the 12 studies yielded consistent results: HRV has prognostic value in tumors, predictive: for both survival and tumor markers [102]. The analysis also showed that the predictive value of HRV may be strong primarily in the advanced stages, the higher initial vagus activity predicted a better prognosis [102]. However, although the vagus effect systemically slows tumorigenesis, its major neurotransmitter the acetylcholine (Ach), promotes local tumor formation [102]. In other study, anti-inflammatory effects of vagus nerve via ACh - $\alpha 7$nAChR. The $\alpha 7$nAChR is expressed on a number of immune cells, suggesting that the vagus may have an effect on the tumor microenvironment and antitumor immunity [58].

Vagus activity may slow tumor progression in pancreatic tumors because it reduces inflammation. A new vagus index was introduced for pancreatic tumors, the neuroimmunomodulation index: $\text{NIM} = \frac{\text{RMSSD}}{\text{CRP}}$, where CRP is the C-reactive protein. Following more than 200 patients with pancreatic cancer, the NIM index was found to have a protective value (relative risk: (0.688)) [62]. Initial higher vagus activity (characterized by HRV) was significantly correlated with a lower risk of death in pancreatic tumors regardless of age and treatment received [160]. The possible mediating role of C-reactive protein (CRP) was tested in non-small cell lung cancer (NSCLC) [8], where the CRP was not found to mediate the relationship between HRV and survival time in patients younger than 65 years, but did not predict overall survival. The NIM index was characteristic also in the study NSCLC; where the NIM index indicated also the protective relative risk. Furthermore, a high NIM index correlates with longer survival [62]. However, for advanced NSCLC, HRV should be used to monitor overall patient well-being rather than to judge survival [161].

Another study with meta-analysis (6 studies analyzed, with 1286 patients) also found that HRV has predictive value in cancer patient survival. Also, higher vagus activity may predict longer survival [162]. Similarly, in a study of hospice patients, it was found that HRV (SDNN value) is a prognostic factor in terminal cancer patients [163].

A meta-analysis of 19 high-quality observational studies [164] shows that higher HRV positively correlates with patients' progression of disease and outcome. The individuals with higher HRV and advanced adapting mechanisms seem to have a better prognosis in cancer progression. HRV appears to be a useful aspect to access the general health status of cancer patients.

A study investigating the role of HRV in gastric cancer patients found that HRV decreased in advanced clinical stages (progression) and correlated with tumor size, tumor infiltration, lymph node metastasis, and distant metastasis. Thus, gastric cancer patients had a lower HRV that correlated with the tumor stage. In this research, they also claim that; HRV may serve as a factor in assessing stage and progression in gastric cancer patients [165]. Based on this, HRV can be a promising biomarker, a prognostic factor in gastric cancer patients.

It was also shown that SDNN value significantly predicted the development of CEA levels in colon tumors 1 year after onset. However, when the patient sample was divided into curative and palliative care, it was found that the HRV-CEA relationship could only be demonstrated in palliative care [166].

In the study of liver tumors, it was found that the indices of HRV, including the previously detailed HF, show a significant correlation with the survival time of patients in patients with end-stage hepatocellular tumors [167]. The HRV significantly positively correlated with survival time in HCC patients [154].

Patients with prostate carcinoma (PC) were examined for vagus tone (with HRV measuring the SDNN and RMSSD). HRV shows a significant inverse correlation with PSA levels at follow-up at 6 and 24 months. This correlation was particularly true in metastatic PC patients [168].

Research on breast tumors (metastatic or recurrent) has hypothesized that high-frequency HRV (HF-HRV), a characteristic of parasympathetic nervous system function, may correlate with survival. Vagus activity was found to be strongly associated with survival (well-predicted survival) [169].

One study examined the association between HRV and brain metastases. Low HRV and a low score on the Karnofsky status rating scale were adverse prognostic factors for survival in patients with cerebral metastases. Based on these, it is thought that HRV may also be a prognostic factor in brain metastases [170].

5. Conclusions

The living cellular structures are energetically open. They need transport of the energy sources in and transport of the waste out. The homeostasis drives the complex system to be balanced, structurally, and dynamically tailored to stochastic (probability-based) equilibrium. Without direct cellular communication (no "social signal"), this organized transport would be missing. The malignant transformation breaks this organized transport and seeks to build up new for the new demands. However, there is a fundamental difference that exists: the healthy construction is driven by the collective signal and seeks to optimize the energy use for the highest efficacy. The malignant structure is driven by the topology and biophysical interactions of the competing cells, irrespective of the efficacy of the energy conversion. This collectivism makes a difference in the geometric arrangement, not only in the cell-cell correlations but the autonomic behavior that forms cells individually.

Different pathophysiological mechanisms and risk factors lead to altered signaling of a common homeostatic pathway indicating various diseases. Consequently, its indication has significant biomedical potential. The homeostatic actions are based on self-similarity, leading to structural changes and information flows, which drive the system's dynamics. Many interacting signals in the complex system produce a noise-like summary, which can be measured in variations of the signal in time-domain, and have a definite frequency distribution in noise power, following inverse dependence, called $1/f$ noise. This noise is meaningful and feasible, regardless of whether the system's signal is deterministic or stochastic. Forcing the $1/f$ signal is a possibility to stimulate the homeostatic control of the system. The heart rate variability (HRV) presents a feasible measuring of the individual status of the patient. The activity and effect of the vagus nerve drive numerous pathways of homeostatic control and are well connected to the HRV too.

Some common mechanisms inhibit the vagus activity in the tumorous situation [171], like the local oxidative stress and DNA damage, the inflammatory reactions, and excessive sympathetic activity. Stimuli may correct the inhibitions, either the vagus-nerve directly or by the compulsory spectrum on the local place of the disease.

The active vagus nerve can reduce the risk of cancer and cardiovascular disease, Alzheimer's disease, and metabolic syndrome by influencing their possible common underlying mechanism. The stimulation of the vagus nerve (VNS) could be a helpful tool fighting to re-establish healthy homeostasis. There is growing evidence that vagus activity slows tumorigenesis, primarily by inhibiting inflammation. Recent studies have shown that neuroimmune modulation increases cytotoxic immunity in the tumor microenvironment. Thus, we appear to modulate the tumor microenvironment and antitumor immunity by influencing vagus nerve activity [58]. It is thought that vagus stimulation, in addition to conventional therapeutic methods, may improve tumor prognosis by aiding in antitumor immunity [58]. The vagus activity and the changes by VNS are well measurable by HRV, and vica versa, the changes of HRV could modify the vagal processes.

Based on the interconnection, measuring vagus activity (primarily by HRV determination) can be a huge help to choose therapies in many diseases. The method has multiple benefits from this safe, complex therapeutic option that improves prognosis in various diseases. It is easy to apply and can be used in conjunction with other routine treatments. It can also be suitable for screening and prevention; it is inexpensive, non-invasive [171]. The HRV controlled VNS is a new direction of the physiologic and psychologic applications [172].

The healthy HRV spectrum shows $1/f$ on average. The averaging is a standard method for investigating diseases, like the evidence-based medicine averages by its various parameters determining the general probability of the studied phenomena. The $1/f$ spectrum is satisfactory for the VNS and HRV, but for personalization, we need differentiation, which means obtaining personal information about the systemic control. However, the frequency distribution shows only which frequencies produce the noise, but no idea about its sequences in time. We had shown the method to analyze the real-time sequences as a basis of personal treatment and follow-up.

The average $1/f$ frequency spectrum is a valuable tool to force the homeostatic arrangement. In therapy, this forcing can be safely and non-invasively administered by modulating a well-chosen radiofrequency carrier and using it to improve the patient's status. The improvement may be measured with conventional checks, but also, the HRV analysis gives information about the achievements of the modulated therapy.

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Conflicts of Interest

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

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