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On the Importance of ATP Energy in Biology with Regard to Viruses

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Abstract

Even today in light of the pandemic spread of the corona virus COVID 19, the debate amongst biologists which concerns whether viruses are alive or not still remains unresolved. This, however, revolves around the argument that viruses cannot produce their own *adenosine triphosphate molecule* (ATP) through metabolism and, therefore, must rely on other living microorganisms that can produce it in order to access the energy that ATP provides upon hydrolysis. It is mainly on account of this distinction that viruses are relegated to an ill-defined area that separates living things from nonliving things. Nevertheless, apparently viruses possess an inherent capacity that enables them to cross this invisible dividing line in order to link up with the ATP molecule through which they sustain their activities. The following presents a review of these issues with regard to microbiology, biochemistry and physics.

Keywords

ATP, Virus, Autonomy, Collaboration, Lineage Formation, Living, Non-Living, Metabolic Whole

1. Introduction

In "*Varieties of Living Things*: *Life at the Intersection of Lineage and Metabolism*" [1], hereafter referred to as "the essay", John Dupré and Maureen A. O'Malley address three fundamental questions: 1) What does it mean for an entity to be living? 2) What is the role of inter-organismic collaboration in evolution? 3) What is a biological individual? And, apparently in light of these questions, their central argument is that "*life arises when lineage-forming entities collaborate in metabolism*". However, their analysis left some questions unanswered about microorganisms and particularly with respect to the biological status of viruses. It seemed that some relevant information was missing that would

more explicitly tie the central argument to the initial fundamental questions. In other words, although the Dupré & O'Malley essay [1] covered biological and evolutionary issues quite satisfyingly, more detailed explanations seem to be required with regard to what metabolism essentially entails in biochemical terms.

For example, the important role that the ATP molecule plays in metabolism was not mentioned even once by Dupré & O'Malley [1] although its discovery dates back to 1929 [2]. Moreover, since *ATP is the energy currency for life*, it can be argued, in order to establish a connection between the above central argument and fundamental question, that the important role played by ATP cannot be circumvented. Fundamentally, there are two ways that a microorganism can be considered, either (a) the organism has the apparatus for metabolism, which means that it has the property or capacity to produce and use ATP for its energy needs, or (b) the organism does not have the apparatus to produce ATP but, nevertheless, has the capacity or capability to partake in existing metabolic processes to satisfy or derive its energy needs. In what follows we will refer to (a) and (b) in light of the fundamental questions (1), (2) and (3) with particular emphasis on viruses.

2. What Does It Mean for an Entity to Be Living? (1)

In his book "*What is Life?*" [3] under the subheading of "*Living Matter Evades the decay to Equilibrium*", Ervin Schrödinger asks "What is the characteristic feature of life? When is a piece of matter said to be alive?" He then answers his own questions saying it is alive "when it goes on *doing something*, moving, exchanging material with its environment for a much longer period than we would expect of an inanimate piece of matter to keep going under similar circumstances" ([3], p. 24). This argument allows that there is an observable or experimentally detectable dividing line between which things can be considered as alive and which things cannot be considered alive. Besides If we now accept the essay's argument that "metabolism, the transformative biochemical reactions that life processes, is a collaborative affair" ([1], p. 2), then it may be considered that (1) has been answered. But (2) must still be considered in context with respect to (a) and (b) in order to establish what role ATP plays in any collaborative endeavors.

3. What Is the Role of Inter-Organismic Collaboration? (2)

In his article "*ATP: The Perfect Energy Currency for the Cell*" [4], Jerry Bergman gives us an excellent account of the role that adenosine phosphates, namely, adenosine monophosphate (AMP), adenosine diphosphate (ADP}, and adenosine triphosphate (ATP) play in biochemical reactions. Here are several points from Bergman's article that are relevant to the present discussion.

- The ubiquitous ATP molecule is used to build complex molecules, contract muscles, generate electricity in nerves, and light fireflies. All fuel sources of nature, all food-stuff of living things, produce ATP, which in turn powers

virtually every activity of the cell and organism ([4], p. 1).

- Energy is usually liberated from the ATP molecule to do work in the cell by a reaction that removes one of the phosphate-oxygen groups to form ADP. When the ATP converts to ADP, the ATP is said to be *spent*. The ADP is then usually immediately recycled in the mitochondria where it is recharged back into ATP ([4], p. 2).
- The enormous amount of activity that occurs inside each of the approximately one hundred trillion human cells are shown by the fact that at any instant, each cell contains about one billion ATP molecules. This amount is sufficient for the cells needs for only a few minutes and must be rapidly recycled ([4], p. 2).
- The total human body content of ATP is only about 50 grams, which must be constantly recycled daily. The ultimate source of energy for constructing ATP is food. ATP is simply the carrier and regulation-storage unit of energy ([4], p. 3).
- ATP is used for many cell functions including *transport work* and moving substances across cell membranes ([4], p. 4).
- ATP manufacture requires several cell processes including fermentation, respiration, and photosynthesis. Most commonly the cells use ADP as a precursor molecule and then add a phosphorus. In eukaryotes this can occur either in the soluble portion of the cytoplasm (cytosol) or in special energy-producing structures called mitochondria. Charging ADP to ATP in the mitochondria is a process called *phosphorylation*. This process occurs in specially constructed chambers located in the mitochondrion's inner membranes ([4], p. 4). A more extensive description of these processes involving the linkage of the budding of enveloped viruses with the energy of ATP can be found in [5].
- Although ATP contains the amount of energy necessary for most reactions, at times more energy is required. The solution is for ATP to release *two* phosphates instead of one, producing one AMP plus a chain of two phosphates called a *pyrophosphate*. How AMP is built up to ATP again illustrates both the precision and the complexity of the cell energy system. The enzymes used in glycolysis, the citric acid cycle, and the electron transport system, are all precise to a degree that they will replace only a *single* phosphate. They cannot add *two* new phosphates to an AMP molecule to form ATP. The solution is an intricate enzyme called *adenylate kinase*, which transfers a single phosphate from an ATP to the AMP, producing *two* ADP molecules. The two ADP molecules can then enter the normal Krebs cycle designed to convert ADP into ATP ([4], p. 6). **Figure 1**, provided by Jerry Bergman [4], shows the relationship that ATP maintains with ADP and AMP.

In light of the above, inter-organismic collaboration between macromolecules and cell organelles, in particular between ATP and mitochondria, cannot be doubted to increase metabolism. Also (a), that a microorganism can produce

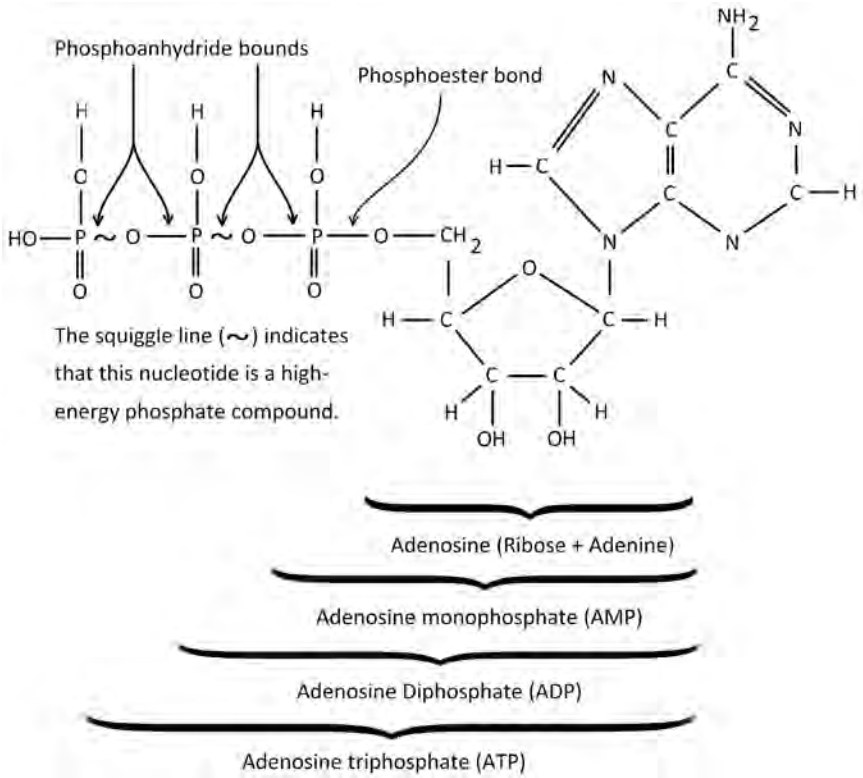

Figure 1. The two-dimensional stick model of the adenosine phosphate family of molecules, showing the atoms and bonds arrangement.

and use ATP, is true. However, how this relates to evolution and (b), how a microorganism can use ATP without being able to produce it, is unknown. Let us now move on to (3) to provide what remains to be said to satisfy (2).

4. What Is a Biological Individual? (3)

The essay [1] indicates that numerous keywords are of particular importance here, namely: *Autonomy*, *Collaboration*, *Lineage formation*, *Living*, *Metabolic whole*, *None-living* ([1], p. 1). Here we will briefly consider how these keywords relate to a biological individual within the context of the essay.

4.1. Autonomy

The essay holds that it is entirely reasonable to view autonomy as centrally exhibited in collaboration rather than ragged independence. If this kind of autonomy is required in order to count as living viruses, which were discovered for the first time at the turn of the 19th century [6], count not only as living matter, but as full-blown entities able to interact with the cell's metabolic capacities ([1], p. 15).

4.2. Collaboration

Although biological theorists assign importance to competition, giving collaboration proper emphasis could provide important insight into the nature of evolutionary processes because it affects how we conceptualize the entities and ac-

tivities central to evolution ([1], p. 14). Many ecological examples of collaboration exist which are at least as compelling as those that highlight competition ([1], p. 16). Collaboration may also include the "mere" coincidence of individual interest, and it is often in the interest of any individual to collaborate at least to some extent ([1], p. 2).

4.3. Lineage Formation

Life, according to the essay, occurs at the intersection of lineage formation and collaborative involvement in metabolism ([1], p. 14). If life is viewed in this way as the result of the intersection of lineage-forming, metabolically collaborative matter organized within different interacting levels, then the smooth transition from the earliest living matter to standard examples of life and beyond all the way up to contemporary ecosystems should be possible ([1], p. 16).

4.4. Living

The essay does not aim to provide an answer to Schrödinger's question "*What is Life*" [3]. Rather the intent is to present a spectrum of biological entities that illustrates why no sharp dividing line between living and non-living things is likely to be useful. Instead, the goal is to offer a view of life that explains why organizations of matter can be described as living ([1], pp. 1-2). A necessary condition for being a living thing is the ability to reproduce, however, it is not obvious that this is sufficient. Living entities must also have the capacity to sustain themselves through biochemical transformations. On that account metabolism can be engaged in autonomously or cooperatively, through interaction with other biological entities ([1], p. 3).

4.5. Metabolic Whole

Life can be seen as something that arises only at the intersection of two features: matter is living when lineages are involved—directly or indirectly—in metabolic processes. The difficulty that arises in the attempt to comprehend life is the observation that the entities which form lineages are not always the same as those that form metabolic wholes. Consequently, it can be argued that metabolism, the transformative biological reactions that sustain life processes, is a collaborative affair. Hence the claim that life is typically found at the collaborative intersection of many lineages, together with the suggestion that collaboration should be seen as a central characteristic of living matter, is also a claim that has implications for how we understand the origins of life ([1], p. 2).

4.6. Non-Living

Many biologists deny that viruses are living organisms, yet viruses are frequently considered to be test cases for the boundary between life and non-life, organism and non-organism, and biology and chemistry, whereby they are most often relegated to the second of each of these category pairs. In that light, viruses are re-

garded as non-living on the grounds that they cannot reproduce themselves autonomously, nor can they metabolize. They can, nevertheless, carry out such biologically impressive activities as entering cells to gain access to the transcription and translation machinery of the cell for their own use. Thus, they are able to move about the DNA from the organism with which they interact. Hence, by exploiting or collaborating with cellular organisms in these ways, they very effectively reproduce themselves and have no requirement of autonomous metabolism [1].

Recalling what was said at the end of (2), namely, that (3) will reveal how things relate to evolution, and (b) how a microorganism can use ATP without being able to produce it, the above shows that the Dupré & O'Malley essay [1] extensively answers such questions within the context of the suggested keywords. However, the above also shows that a very important keyword or term, namely ATP, must be added to the list of keywords to achieve some clarity about what role in metabolism, and in particular in collaborative metabolism or metabolic processes, ATP plays in biology.

This is also of particular importance with regard to the status of viruses. They can only keep reproducing for a prolonged period of time, as Schrödinger has it [3], if they have access to energy, which only ATP can provide for them. Moreover, including ATP as a major key-term emphasizes the importance of the distinction between (a) having a metabolism and (b) partaking in metabolic processes, rather than de-emphasizing this.

Since processes involving the adenosine phosphates AMP, ADP, and ATP are central to metabolism, it can be concluded that viruses rely on this for their external source for energy more so than any other entities considered in this review. In short, ATP is food for viruses. It is the energy of ATP that sustains their activities and keeps them doing what they were meant to do, which is to reproduce and thus to survive. And for that, viruses do not depend on what we believe or think with regard to whether they are alive or not.

5. Conclusions

With regard to the essay's central argument that *life arises when lineage forming entities collaborate in metabolism*, it seemed that we needed a more explicit description of what metabolism in biology entails. By taking a close look at the three fundamental questions (1), (2), and (3) and by taking (a), and (b) into consideration, it can be shown that if the role of ATP is also accounted for, then a more straightforward description of metabolism in biology can be produced. The inclusion of ATP in this discussion does not diminish the essay's central argument, but rather strengthens it by providing the missing link between the central argument and the three fundamental questions.

Moreover, by adding ATP to the discussion, the important role that viruses play in biology also becomes more explicit. Furthermore, if one views ATP as the perfect energy currency for the cell, then that currency can best be explained

with regard to physics. It is not difficult to calculate that the energy liberated by the conversion of 1 mole of ATP to the energy of one molecule of ATP amounts to 6.64×10^{-20} joules, which can be related to the standard unit definition of 1 eV (electron volt) which is equivalent to 1.60×10^{-19} joules of energy.

One may assume that these infinitesimally small amounts of energy are insignificant but, when one considers that a virus must deal with its needs for energy to sustain its activities by picking up each infinitesimally small quantum of energy one at a time, the provision of energy by a single ATP molecule is not insignificant, given that only two and a half conversions from ATP to ADP are required to generate 1 eV of energy. And, of course, the electron volt plays an important role in measuring electron transport. Further information of how ATP levels of living cells can be visualized and measured can be found in [7]. In short, by looking at things in terms of biophysics, it would appear that there is no longer any reason for viruses to be placed separately in the gray area of the non-living, given that they use the energy provided by the ATP molecules of living cells in order to reproduce and survive. Thus, viruses associate in symbiosis with living cells. Consequently, it can be concluded that to reproduce and survive, viruses developed the ability to interact in symbiosis with living cells to take advantage of their ATP energy production mechanism in a non-collaborative parasitic manner that often leads to the death of the cells but, this also ensures the survival of the viruses' lineages.

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Conflicts of Interest

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

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Quantum States in Templated Biological Processes

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Abstract

Living matter is characterized by its variegated potential energy landscape possessing a proneness to continually absorb externally supplied energy. This enables it to ascend from its momentary energy minimum state to one of its myriad barriers only to subsequently descend to a new minimum with a potentiality to perform new functions or processes, in the while exuding energy (mainly in the form of heat). As in studies of molecular intersystem crossing, the jumping processes are describable in terms of quantum states. In this work we derive the low energy quantum states for those three templated self-assembling processes, self-replication, metabolism and self-repair that are commonly regarded as distinguishing animate from inanimate substance. The outcome of each process is a new, long-living, stable molecular aggregate characterized by its specific conformation, comprising a host of micro-states associated with sub-conformations and patterned upon the template. The provenance of these newly-formed states is obtained here by a unified formalism for all three processes, based on a Hamiltonian, constructed in an abstract Hilbert-space framework, whose essences are bilinear coupling terms in the Hamiltonian between the template and the bath, as well as between the reactants and the bath. Treating these terms by second order perturbation, one finds in low lying quantum states an alignment between the template and the product, somewhat analogous to the Kramers-Anderson superexchange mechanism, with the bath replacing the bridging anion and by exploitation of the decohering due to the randomness of the bath. The idea underlying this work, recurrent in the biological literature and here expressed in a Physics, Hamiltonian framework, is the correlative unity of the whole biological system comprising multiple organs.

Keywords

Living Systems, Self-Organization, Hilbert Space, Molecular Conformation, Decoherence, Pseudo Jahn-Teller-Effect

1. Introduction

The dichotomy of living *versus* inanimate matter is one of the central puzzles in our understanding of the world around us and as such has occasioned a wide literature [1]-[7]. Besides constituting an intellectual challenge (reflecting also on ideologies [8], beliefs [9], life's meaningfulness [10]), it has bearings on very practical issues, like robotics [11], biomimetics [12], artificial intelligence [13] [14], quantum computing [15] [16]. It is commonly asserted that living systems are distinguished by their faculty for self-replication, metabolism and self-repair (the first of which is accredited to Kant). In this work each faculty is formulated in a quantum mechanical framework. The limitations of such undertaking are so obviously manifold that they need not be stressed at the outset, but will be noted as we go along. The basic rationale is the recognition that biological systems are definite molecular aggregates (in Schrödinger's terminology "aperiodic crystals" [1]) with well defined conformations. The meaning of conformation is the mode of mutual attachment between molecules in an organ, including their relative orientations, but here we include also electronic and vibrational states. In short, all degrees of freedom (dof).

In actual biological systems conformations possess a large measure of stability or permanence, measured erstwhile by the free energy excess of the next, higher lying conformation. Thus in functional proteins this excess in the unfolded state relative to the native, folded state is about 2500 K in temperature units, so that at room temperatures at most only a fraction 0.00025 of proteins is unfolded [17]. The high conformational stability of DNA is at the root of anthropology analyses of human and animal skeletal remains, lifeless over several millennia (a presumed 700, in the case of a horse in Yukon permafrost in Alaska). The stability of conformations implies that they are residing in a low lying quantum state. Below it is argued that this is a mixed state, composed of micro-states identified as those arising from numerous multi-stable sub-conformations [18] [19] [20]. Under assumption of ergodicity, this entails a decohered motion of a particular organ between its micro-states. The status of states in sub-conformations ("conformational substates", CS) belonging to the same conformation (e.g., to the folded form of proteins) and crucial for their signalling and functions, will be discussed in subsection 3.2, below.

In a unified formalism for each of the three above mentioned conformational changes of biological organs, the present work shows how each CS in the outcome organ is parented by the analogous CS in the template. This is achieved by deriving low-lying eigenstates for the template-product organ pair from a postulated Hamiltonian, whose notable features are the organs' bilinear interaction terms with the environment (the "bath"). Treated perturbationally, these terms align corresponding states in the Hilbert spaces of the pair.

It is stressed that the theory here outlined does not address the mode of functioning of the biological units, an activity that takes place under conditions of non-equilibrium, but only their mode of assembly onto a quiescent form out of

their constituents. The theory has thus some methodological similarities to what is practised in CASP (Critical Assessment of protein Structure Prediction), in which the task is to predict three dimensional structures of proteins on the basis of submitted various amino acid sequences [21]. Earlier successes in CASP competitions, mainly through the intense computational efforts of Computational Molecular Physics (CMP), have been summarized in [22] and a more recent one described in [23]. Full and partial applications of quantum mechanical methods to biological systems, pioneered in [24], have been comprehensively reviewed in [25]. Nevertheless, the complexity of the molecular arrangements is frequently countered by adoption of a classical or semi-classical approach.

Adjacent to the present theory of creation of organs from a template, is the subject of morphogenesis, addressing the emergence of form in living systems. In a monumental work, structure and patterns in plants and animals were studied from a "physico-mathematical" viewpoint by D'Arcy W. Thomson [26], in which a quotation epitomises also the present work [27]. Deviations from symmetrical forms, due to random disturbances and fortified by activators ("evocators") and inhibitors, were treated with methods of Physical Chemistry by Turing [28]. Recent ramifications of morphogenesis, particularly in the direction of embryogenesis, incorporate a host of assistant actors [29]. A detailed sequential description of the latter is provided in [30].

The following introductory remarks refer mainly to the first of three processes treated here, but are valid for the other two, as well.

In a self-replicative process the template (T) unit (composed of possibly one, but mostly several interwoven molecules) gathers up from the surrounding molecular Zoo, in biological literature named "library", exactly the same molecules of which itself is composed and arranges them with the intermediary of enzymes in a new unit, the replicate (R), that assumes the same (or very nearly so) state as itself and (in case of contact or close adjacency) detaches itself from it to continue with separate existences. (Cf. childbirth as an example or an analogy).

From the Physics viewpoint, in the past self-replication (SR) has been treated as a process, subject to laws of non-equilibrium Thermodynamics or Dynamic Statistical Mechanics (e.g., [31] for a recent account); here it is treated by consideration of the microscopic entities of which it is composed. As such, these are subject, like all other material entities, to Quantum Mechanics (QM), and as a consequence require description in terms of the basic brick-stones of QM, namely "quantal states". It is upon these that the followings rest. SR being a process, implies by definition "transitions" and more precisely in QM: transitions between the states pre- and post-SR; their description is avoided here due to the fact that the status of transitions in QM (termed as "Measurements") is problematic and controversial.

1.1. Sub-Conformal Protein Motion: Phased or Decohered?

For proteins (and not for them alone) it is now well established that a profile of

the potential energy landscape along an interaction coordinate consists of a great number of potential wells of similar depths (energy-wise differing by less than room temperature and separated by barriers of energy heights exceeding 800 K) [32] [33]. In their quiescent mode, proteins responding to temperature caused fluctuations move about these wells and the important question arises whether the quantum state of a mobile protein is phase observing, such that in the superposition (sum) of the components belonging to the different wells there persist definite phase relations, or is it a "mixed state" in which the weights of components are fixed statistically (possibly by a Gibbs distribution function for a macro-canonical ensemble), but not the phases. In the latter case, assuming ergodic behaviour in the protein, the time spent by the molecule in each well is also by the same distribution.

The issue of tunneling *versus* barrier-jumping has been at the basis of the anomalous temperature dependence of the specific heats at low temperatures of some glasses, whose state has formed a prototype for that in proteins [32]. This was clarified in [34] [35] by considerations of tunneling in two level systems, which is of importance at low temperatures and there alone [34] [35] [36] [37]. Tunneling in biological molecules was the subject of Colloquium in the late seventies [38], in which the question of phase-conserving *versus* decohered state outcome of the processes was left unanswered.

In the former, passage between the wells may be promoted through temperature effects raising and lowering adiabatically the wells, thus enabling the protein to tunnel across two or more wells coherently. Movement in the mixed state arises by the more common barrier jumping, Marcus-type thermally activated mechanism. If adjacent wells belong to different electronic states, then the electron-vibrational mechanism (associated with an energy-gap law behaviour and involving a "promoting" coordinate factor [39] [40]) is applicable, otherwise only vibrationally induced transitions operate [41]. In either event, the randomising mechanism inherent in temperature activation ensures that in the state resident in the new well there is no remnant of the starting phase. The conclusion that the stable conformation represents a mixed state with respect to the SC states, with no phase coherence among these, so that the different states within the ensemble can give rise to different H-tunneling probabilities. This is of importance for the present theory, in that each SC state in the template gets individually entangled with a state (or states) in the replicate, rather than as a coherent superposition of SC states.

It is of interest to remark that Bersuker has argued in various publications, e.g., [42], that when a point of instability separates the wells, there must necessarily be different electronic states to which the different wells belong, known as the pseudo Jahn-Teller effect. The outcome of such occurrence is the drastic reduction by several orders of magnitudes of the pre-exponential factor in the rate expression from a frequently assumed value of inverse nano- or femto-second [1]. Typical inter-well transition times in some enzymes were indeed estimated to be as high as milliseconds [20].

1.2. Self-Assembly

The three transformations treated here are those for the normal flow of biological information: DNA can be copied to DNA (DNA replication), DNA information can be copied into mRNA (transcription), and proteins can be synthesized using the information in mRNA as a template (translation), known as the central dogma of biology [43] and predicated at each stage upon the existence of a template. A related subject not considered here is the non-templated self-assembly of (frequently large and biologically significant) molecules [44] [45], in which the final product is not replicated. Successes in this field have strong repercussions in the search for primordial bio-genetic mechanisms [46] [47] [48] [49].

2. Formalism

Notation

Let the full biological system under consideration be considered as composed of a mutually exclusive set of organs, designated generically X, each organ possessing an arbitrary number of molecules, describable by NX_B bosonic and NX_F fermionic degrees of freedom (dof). Although the numbers of quantum states (energy eigen-states, deemed non-degenerate) of these dof are in general infinite (enumerably such for bound states and otherwise for continuous states or for translational degrees of motion), we consider only a finite though arbitrarily large number of these, MX_B and MX_F respectively, so that the Hilbert space of each organ is of size $NX = NX_B^{MX_B} * NX_F^{MX_F}$. The whole Hilbert space is the direct product of these organs. Next, each organ is distinguished by a capital letter with eigenstates labelled with the corresponding greek letter, as follows:

1) The template organ T, with state kets $|\tau\rangle$, characterized by stability and being well organized to carry out various tasks.

2) The template's sister organs S (with kets: $|\sigma\rangle$) composed of the same types of molecules and in the same configuration and state as T. These organs number N_S.

3) The candidate for replication R ($|\rho\rangle$), also consisting of the same types as the template, but initially in different states, e.g. dispersed in the system.

4) A different set of molecules from the former, out of which some new, product organ is formed, designated P ($|\pi\rangle$).

5) The full biological system excluding those items in the above, constituting the bath B ($|\beta\rangle$), characterized by the random amplitudes and phases in the states of its constituents.

We now order the points in Hilbert state of each organ according to rising energy values (supposed to be non-degenerate), with the energy ground state labelled 0. We thus obtain a vector for each organ and the direct product of the five vectors for the whole system. We write this

$$|\Psi\rangle = |T\rangle|S\rangle|R\rangle|P\rangle|B\rangle \tag{1}$$

A partial direct product, exclusive of $|X\rangle$ will be denoted $|\Psi\rangle_X$ and that

exclusive of $|X\rangle|Y\rangle$, $|\Psi\rangle_{XY}$.

Members of mammoth direct product in Equation (1), numbering $\Pi_{X=T,S,R,P,B}(NX)$, will form the bases for the Hamiltonian matrix to be formulated. The Hamiltonian operator is a sum of the self-energies of the organs and of coupling terms between the first four organism types and the bath. The latter terms will be treated by perturbation theory, but their entering the formalism is the foundation stone of the theory. Conceptually, they reflect the unity and cohesion of the full living system. We thus start with the Hamiltonian operator

$$\hat{H} = \sum_{X=T,S,R,P,B} \widehat{H_X} + \sum_{X=T,S,R,P} \widehat{H_{XB}} \tag{2}$$

$$\widehat{H_X} = |\Psi\rangle_X \sum_{\xi} h_{\xi} |\xi\rangle\langle\xi|_X \langle\Psi|, \ (X = T,R,S,P,B) \tag{3}$$

$$\widehat{H_{XB}} = |\Psi\rangle_{XB} \sum_{\xi\beta} g_{\xi\beta} |\xi\rangle\langle\beta|_{XB} \langle\Psi| + c.c., \ (X = T,R,S,P) \tag{4}$$

The operators in the second line enter the Hamiltonian matrix as diagonal terms; those in the third line as off-diagonal terms.

(Remark on the formalism: A more natural description of the systems would be within a second quantization formalism. But then fermionic and bosonic operators would have to be distinguished, thus doubling the nomenclature. An added remark is that in a previous, much more simplified, formulation of the theory [50] we included a further many component system, entitled the "library" which was then incorporated into a Hamiltonian of a few $\approx 2^5$ order and solved numerically. As pointed out there, their inclusion did not qualitatively affect the outcomes. Here they are included in the bath. One may also add for clarification, that, with the bath being considered homogeneous and of limitless extent, one may eliminate from the formalism the space-translational dof, keeping only those for the inter-molecular distances.)

With this we are ready to formulate the three salient biological activities: replication, metabolism and repair, in turn.

3. Self-Replication

Here one considers two different realizations of the T-R system the template (T) and the (potential) replicate (R), *each containing the same molecular set* and therefore the same set of dof. We thus obtain two state vectors (kets) of size N each, designated

$$|T\rangle, |R\rangle \tag{5}$$

with representatives T_τ and R_ρ, respectively.

$$T_\tau = e^{i\phi_\tau}\delta_{\tau,\tau_{gr}}; \ \tau_{gr} := 0; \ R_\rho = \frac{1}{\sqrt{R_{mix}}} e^{i\phi_\rho}\delta_{\rho,\rho_{R_i}}, \ (R_i = 1,\cdots,R_{mix}) \tag{6}$$

In the template T_{gr} is an eigenstate, being *one or another CS of the conformational energy ground state, e.g., of a folded state for a protein*. The (potential) replicate is in one of its R_{mix}'s state, being a mixed state with equal likelihood of being in any of these. Though the concise notation does not reveal any great dif-

ference between the states of T and R, the construction of the state vectors from all degrees of motion allows us to represent the template state by a localized compact and ordered arrangement of molecules and the (potential) replicate state by a set of isomerically different and even dispersed, irregularly spaced and oriented molecular aggregate. The "miracle" is that the formalism shows the way to arrange the latter into the likeness of the orderly agglomerate of the template.

Additional to their being in different eigen-energy states, the difference between T and R is also reflected in their initial entropy values being 0 (for T) and $\ln R_{mix}$ (for R). The entropy difference is due to the environment (the "bath") being regarded homogeneous and of unlimited extent, in which the freely floating molecules can take up any position, while in the attached situation, they lack this freedom. The gain in free energy resulting from a decrease of entropy at room temperature, incident upon attachment, relative to a free movement for particles at millimolar concentration has been estimated as 5.5 kcal/mol, while for the freezing of rotational freedom the free energy gain was 0.7 kca/mol [45].

3.1. Single Subconformation

3.1.1. A "Superexchange" Analogy

Let us consider for a start the case when there is a single well in the conformation; the realistic multi-stability case is taken up in subsection 3.2. For the template to have the capability of self-replication, it must have the property of stability. This means that

1) T is in ground state $\tau = 0$, and to avoid excitation by the rest of the organism or by thermal fluctuation,

2) its energy relative to the next excited state must be negatively much larger than the scaled temperature: $|h_0| \gg k_B T, |h_1 - h_0| \gg k_B T$.

(k_B being the Boltzmann constant and in this context T the temperature. Henceforth, $k_B T$ will serve as the energy unit.)

It needs to be remarked that for identically labelled components of T and R, $\tau = \rho$, one has $g_{\tau\beta} = g_{\rho\beta}$, since both coefficients couple identical states to a given bath state. With this property and having regard to the random phases of the bath state amplitude we can show, incurring some approximation procedures. that the T-bath and R-bath coupling terms in Equation (4), taken together, force the replicate to a state identical to that of the template. To demonstrate this, we treat the following, arising from two terms in Equation (4), perturbationally.

$$\widehat{H_{TB}} + \widehat{H_{RB}} := \widehat{H_{TR-B}} \tag{7}$$

The first order perturbational correction to the energy due to these terms

$$\delta^{(1)} E_\Psi := {}_{TR}\left\langle \Psi \middle| \widehat{H_{TR-B}} \middle| \Psi \right\rangle_{TR} \tag{8}$$

vanishes due to the randomness in the bath variables. The second order correction is now manipulated as follows:

$$\delta^{(2)} E_\Psi := \frac{\sum_{exc} \left| \left\langle \Psi \middle| \widehat{H_{TR-B}} \middle| \Psi \right\rangle \right|^2}{E_\Psi - E_{exc}} \tag{9}$$

Approximate now by replacing the denominators by their (negative) average $-|\nabla E|$ and apply closure to get

$$\delta^2 E_\Psi \approx -|\nabla E|^{-1} \langle \Psi | \left[\widehat{H_{TB}} + \widehat{H_{RB}} \right]^2 | \Psi \rangle \tag{10}$$

Opening the square bracket, one finds that the squared terms contribute only negative constant terms to the T-R system. However, the cross terms give after tracing over the P, S, B organs' dof

$$-\frac{1}{|\nabla E|} \langle T | \langle R | \left[\sum_{\tau\rho\beta} g^*_{\tau\beta} g_{\rho\beta} | \tau \rangle | \rho \rangle \langle \rho | \langle \tau | \right] | R \rangle | T \rangle + \text{complex conjugate} \tag{11}$$

whereas for $\tau \neq \rho$ the sum decoheres due to the random nature of the bath, for $\tau = \rho$ in the sum the product terms $g^*_{\tau\beta} g_{\rho\beta}$ are necessarily positive $|g_{\rho\beta}|^2$, since both the template and the replicate are composed of the same set of molecules and the interaction with the bath is identical. Adopting now from the theory of electron-paramagnetic resonance a further approximative procedure, known as the "Effective Hamiltonian formalism", we can employ the term inside the bra-kets as an interaction term in the T-R Hamiltonian. Explicitly

$$\delta H_{T-R} = -\sum_{\tau\rho} |\tau\rangle |\rho\rangle W_\tau \langle \rho | \langle \tau |; \; W_\tau := -\frac{1}{|\nabla E|} \sum_\beta |g_{\tau\beta}|^2 \tag{12}$$

The direct effect of this term is the tendency to align in the ground state the replica state with the template state. As by construction and its stability (expressed by $h_{\tau=0} \gg 1$ for the template's state), the replicate's state will also be this state, provided only that algebraically

$$W > h_\rho, \text{all } \rho \tag{13}$$

With the inclusion of the term gained from the second order perturbation and after elimination of the bath' dof, the Hamiltonian for the T-R system reads

$$\begin{aligned} \widehat{H_{T-R}} \approx & -\sum_{\tau\rho,\tau'\rho'} h_\tau |\tau,\rho\rangle \langle \tau',\rho'| \delta_{\tau,\tau'} - \sum_{\tau\rho,\tau'\rho'} h_\rho |\tau,\rho\rangle \langle \tau',\rho'| \delta_{\rho,\rho'} \\ & + \sum_{\tau\rho,\tau'\rho'} \left[g_{\tau\rho,\tau'\rho'} - W_\tau \delta_{\tau,\rho} \delta_{\tau',\rho'} \right] |\tau,\rho\rangle \langle \tau',\rho'| \end{aligned} \tag{14}$$

The first requirement upon this expression is the large value of $|h_0| \gg 1$ in the first sum, thereby ensuring that in the lowest lying energy state of the (diagonalized) H_{T-R}, the target ground state $\tau = 0$ will be predominant. Next is the requirement for a large diagonal term $W_0 \gg 1$ in the square brackets of the second line, that has the role of making the

$$\rho = \tau = 0 \tag{15}$$

state govern also the replicate in the T-R ground state, and this under the proviso that in the square bracket the accompanying term $g_{\tau\rho,\tau'\rho'}$ is substantially less. The criteria for SR can thus be quantitatively formulated through the inequalities on a temperature energy scale ($k_B T = 1$)

$$h_\tau \gg 1 \text{ for } \tau = 0, |h_\rho| = O(1) \text{ all } \rho, W_0 \gg 1, W_0 > |g_{\tau\rho,\tau'\rho'}| \text{ all indices} \tag{16}$$

Here the second relation ensures that self replication occurs as an outcome of

the process of switching on the interactions and not due to the intrinsic property of the replicate. The physical meanings of the relations are for the first: the stability of the template; for the second: a propensity of change in the initial state of the (potential) replicate; for the third: an effective interaction with the bath; finally, the low availability of alternative channels for changes in the replicate.

The similarity of the formalism with Kramers' and P.W. Anderson's mechanism for superexchange [51] [52] will be noted, with the bath replacing the bridging anion and exploitation of the randomness of the former. The aligning factor W_τ, Equation (12), has its counterpart in the "attractive coupling" expression (based on third order perturbation) of Anderson following his Equation (19) in [52].

3.1.2. An Illustration

The aligning effect of the second order perturbation term can be seen in an algebraically solvable model, in which the template and the replicate have each two states. With the choice of a large value for the template's self-energy $h_T = 24$, the calculated alignment of the replicate in the ground state is contour plotted in **Figure 1**, as function of W as the abscissa and h_R as the ordinate. In the blank bottom-right region the alignment is complete, while in the blue upper-left part the alignment is well-nigh zero. The diagonal dividing line is $|h_\rho| = W$, a line of bifurcation, along which the aligning and non-aligning states are co-degenerate. (A more detailed study of this bifurcation, potentially giving rise to criticality, is left to a future work.)

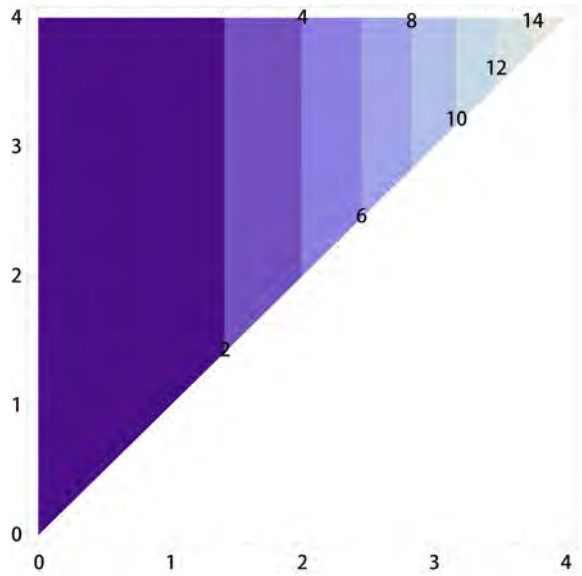

Figure 1. Alignment of the replicate with the state of the template plotted with $x = W$ (the second order bath coupling strength); $y = -h_\rho$ (a negative, anti-aligning replicate self-energy). There is full alignment in the blank triangle, minimal alignment in the blue regions, with more smallness on the left. The gradations show changes in the minute alignment probabilities for the non-aligned region roughly in units of 3×10^{-4} decreasing towards the left.

3.2. Multiple Subconformations, SC

While the foregoing theory related to a single ground state SC for both the template and the replicate, in reality there are a number of these, designated subconformations (SC), belonging to the same generically termed "conformation", e.g., the folded state for proteins. Moreover, these SC are vital for the functionings of the organ, insomuch that an external signal, as also thermal fluctuations shunt the organs between the SC, while still residing in the basic conformation. As the energy difference between SC are much smaller than between different conformations, they will be populated to varying extents and the interconversions are governed by the heights of the barriers between the subconformations [18]. Likewise, the activity of the protein, like H-tunneling, may send it from one to another SC. More radical and lasting effects were noted in [19] under the heading of "evolvability", with this taking place at a faster rate in RNA than in proteins.

An examination of the foregoing theory shows that the results of Section 3 hold for each SC separately, in the sense that when the template resides in one of its multi-stable states, it will drag along the replicate to an identical multi-stable state. The protein being in a mixed state of SC, there is no phase relation between them. The process is illustrated in Figure 2. Formally, one extends the notation of 0 for a unique ground state to $0',0'',0''',\cdots$ for the set of multi-stable states, and replace the criterion in Equation (15) to

$$g_{\rho\beta} = g_{\tau\beta},\ \rho = \tau = 0',0'',0''',\cdots \tag{17}$$

4. Metabolism

Here the situation differs from the one for SR, in that the physical organ performing the metabolic action (which due to the scarcity of symbols will still be termed "template, T" and its Hilbert space labelled by τ, in spite of the risk of misnomers) gathers up from the "library" a set of molecules different from those that itself is composed of, organizes, transforms (metabolises) them to a new aggregate of a specific form and potentiality to perform a specific task and—then

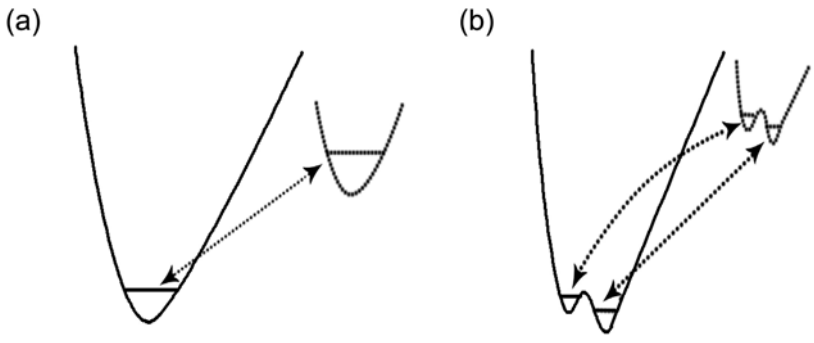

Figure 2. Replication to a CS. (a) For a single CS in the conformation, the unique ground state in the template (lower well) is replicated onto the replicate (upper well) to form the combined ground state; (b) For multiple CS (with only two drawn) each CS in the template is separately partnered by the corresponding CS in the replicate.

sends the away. In the present formalism the product is labelled P and the components π. The most notable examples are for T = DNA and P = a protein.

The required changes in the formalism set out for SR are, apart from the obvious replacements of $R \mapsto P, \rho \mapsto \pi$, that the Hilbert-spaces of T and P are different. The main step now is the inclusion of the perturbative terms

$$\widehat{\nabla H_{TB}} + \widehat{\nabla H_{PB}} := \widehat{H_{TP-B}} \tag{18}$$

in the Hamiltonian operator. When the effects of these are estimated by second order perturbation theory and following the approximative procedures (constant, average energy denominators, random phase dissipation, effective Hamiltonian description) made in Section 3, one obtains the following equalities that are necessary and sufficient for the creation of a new metabolic entity, *fully specified*, apart from phase, by the Hilbert space index π_P:

$$g_{\tau_{gr},\beta} = g_{\pi_P,\beta}, \text{ all } \beta, \text{ the bath-state index} \tag{19}$$

This relation ensures that all bilinear terms in the effective T-P Hamiltonian term add up constructively and negatively. Analogously to the result for SR, when this term has a large absolute value, one obtains for the T-P *ground state* the new combined state made up of the original template state τ_{gr}, as well as of the new product state π_P, a metabolic addition to the organs of the biological system. The identity and form of this product state are specified by that, that it is the state $|\pi_P\rangle$ for which the equalities in Equation (19) hold. (By implication, if these equalities do not hold, the template does not metabolize and is left to do other tasks.)

At this point it needs to be noted that (in contrast to the case of SR, in which the two members of Equation (19) related to the states of identical molecular systems, in the template and its replicate, and had clear intuitive justification) the provenance of Equation (19) is not clear. It may be related to some underlying unity in the full biological system, T-P-B, possibly beyond the reach of human inquiry. Nevertheless, the foregoing analysis is of value as a comprehensive descriptive formalism within a quantum mechanics frame.

5. Biological Repair

Here matters are more complicated, since there are three stages to the process: the recognition of damage, (frequently) sealing and healing (regeneration) [12]. For each stage questions arise as to how the information reaches the organ, where it originates, what prompts the need and mode of action to be taken, etc.? These questions are not here answered. There exists, though, for the threshold timing of wound recognition in cells an estimate of 1 - 10 s, provided in [53], which discusses in detail two instances of damage: a cell damage due to *puncture* of *Xenopus oocytes* and the *loss* of oral apparatus in *Stentor coeruleus*.

The latter form is clearly the more radical one, exemplifying that class of damage in which a loss of an entire organ has taken place (the loss of flagellum in Chlamydomonas is a frequently quoted example, as again in [53]); even here,

too, some repair or adjustment is frequently brought into play. In addition to repair, or as an independent side effect, a genetic regulatory mechanism provoked by organ changes has also been noted in some cases [54]. Thus in observations in amphibian embryos of polyploidy (the presence of more than two chromosome sets, frequent among plants) changes in cell shapes were noted, thereby maintaining the normal form of organs. Remarkably, the theory presented in the following subsumes even this radical class of damages, the loss of an organ, though it does so in an extremely abstract way. A criterion for catastrophic, irreparable damage types also emerges from the formalism.

5.1. A Majority Rule

The guiding idea for recognition of aberrations by biological organs and their subsequent elimination may be termed "the democratization of the organs". It postulates that any time of maturation there are a number of organs (cells, proteins, etc.), entrusted to carry out identical tasks, and at stages of normalcy possessing the same structure and occupying the same quantum state. Normally, this is their ground state (0). However, it can happen that some external factor removes temporarily one or a few organs from that state forcing it into another damaged state, but leaving the majority of organs in their original ground state. At this stage, there enters the interaction between the organs, by which the sister organs notify the damaged state of its aberrant status. At that instance, the healing or repair process begins.

This arises from the mutual interaction between the damaged organ and its sister organs, mediated by the coupling of the organs to the bath. As in the previous Sections 3 and 4 this coupling is treated in second order and with tracing over the bath states. Due to its entering negatively the Hamiltonian, the resulting coupling drives the damaged organ to an alignment with the healthy sister organs' state, namely to its pre-damage ground state. Needless to re-emphasize that the theory (which is formulated in terms of states, not of processes) does not explain the mechanism of the events (recognition, repair), only their outcomes. The following separates the stages of the repair process.

5.1.1. Damage

We recall from Section 2 that the stability or permanency of the template T is ensured by that its self-energy h_0 in its ground state (labelling $\tau = 0$) is negative and numerically large. We now adopt the symbol D for the organ undergoing damage and δ for its states (the ordered Hilbert-space points), so that again $\delta = 0$ denotes the ground state of D prior to its repair. As parts of the living system, additional to T there are N_S sister organs labelled n tasked with the same function as T, identical to it, all residing in their ground states.

The damage done to T is expressed by the application of a unitary, transformation matrix $D_{\delta,\tau}$ to the template T. During its damaged state the organ's states are

$$|\delta\rangle = \sum_{\tau} D_{\delta,\tau} |\tau\rangle \tag{20}$$

with self-energies

$$E_{\delta} = \sum_{\tau} \left| D_{\delta,\tau} \right|^2 h_{\tau} \tag{21}$$

Clearly the ground state energy of this, $E_{gr} \approx -\left|h_0\right| \left(D_{gr,0}\right)^2$ is different from that of the undamaged template $-\left|h_0\right|$. Moreover, the new damaged ground state of the organ is $\sum_{\tau} D_{gr,\tau} \left|\tau\right\rangle$, different from $\left|0\right\rangle$. (The difference in the state, arising from the damage can be of any form or extent; e.g., it can even represent the detachment of part of the organ. This follows from the completeness of the Hilbert space, which includes all possible states and configurations of the ensemble of molecules constituting the organ.)

5.1.2. Repair

The repair is achieved by the damaged organ receiving feedback from the rest of the sister-organs in the system. As in the previous Sections 3 and 4 the correction arises from the second order perturbational treatment of the interaction terms of the template and its sister molecules with the bath

$$\widehat{H_{DB}} + \sum_{n=1,\cdots,N_S} \widehat{H_{S_n B}} \coloneqq \widehat{H_{DS-B}} \tag{22}$$

similar to Equation (7), but a sum over all sister organs in the second term on the left. It is important to realize that the organ-bath coupling terms $g_{\tau\beta}$ in H_{DB} are not changed by the occupation of the states, since the Hamiltonian depends only on the identity of molecular components and not on the temporary occupancy of the states. This identity is not changed by damage. Therefore

$$\widehat{H_{DB}} \equiv \widehat{H_{TB}} \tag{23}$$

Carrying out the second order perturbation as heretofore, one is left with a (negative) coupling of the form

$$\delta H_{D-S} = \delta H_{T-S} = -\sum_{\tau\sigma} \left|\tau\right\rangle \left|\sigma\right\rangle W_{\tau}^{D} \left\langle\sigma\right| \left\langle\tau\right|; \; W_{\tau}^{D} \coloneqq -\frac{N_S}{\left|\nabla E\right|} \sum_{\tau\beta} \left| g_{\tau\beta} \right|^2 \tag{24}$$

Meaning: The combined effect of the healthy sister organs, residing in their ground state $\sigma = 0$ drives the damaged organ back to its original ground state $\tau = 0$. Repair has been achieved. In fact, this process of self-repair is equivalent to that in self-replication, since the same molecular entities are involved, the difference being only that here a number (N_S) of organs reproduce their own image.

(As a corollary one may note that with a lethal damage, when the number of undamaged organs N_S is insufficiently large, repair may not take place and the system becomes defunct. This can also occur when the system is small and cannot provide appropriate feedback.)

6. Couplings

In the foregoing formalism an essential and critical role was played by the interaction terms (of the type $g_{\tau\beta}$) between the biological entity and its surround-

ings. Whereas it is usual to deal with these interactions under the amorphous title of "weak thermal interaction", here they were subject to precise, detailed equalities. Moreover, the entities so being coupled were not confined to the immediate neighbourhood, but were rather spread out over the fullness of the biological space. As already noted elsewhere, organisms' (and also cells') functionality and even survival is not an intrinsic property of the organism (or cell), but is due to interactions between a large number of cells [55]. This property is at the basis of the formalism.

A quotation (with permission) from [55] (p.72) amplifies this, as follows:

"A cell is the basic unit of life and all living organisms are composed of one or more cells. The capacity of organisms to adapt to changing and often hostile environments, tolerate limited failures and heal damaged organs is not because of the robustness of individual cells, but because of the interactions between large numbers of cells. A cell is able to divide into two daughter cells, emit chemicals to the surrounding environment, and actively deform by applying physical forces across its walls. Different chemicals within and around the cell control these actions. A cell can sense chemicals on its walls, as well as in its environment. The nucleus of the cell contains DNA, which encodes different genes that have been retained through evolution. A gene is activated when a certain condition is true. This condition could be a critical concentration level of a chemical or a set of chemicals that the cell possesses or that the cell has sensed. When a gene is activated it may cause certain cell actions, which could result in the turning other genes on or off."

However, question arises as to the origin and nature of these couplings?

Electromagnetic, covalent and exchange forces (or in phenomenological terms: Coulomb, hydrogen bonding, van der Waals and hydrophobic interactions) are prevalent in chemical bondings and as long as the distance dependence of the coupling coefficients is not clarified, it is not possible to answer the question above. It is necessary to note, though, that the coupling terms connect up the organ with the bath (manifest through the bath index β in the coupling coefficient), and the bath environment is regarded as homogeneous and of unlimited extent, devoid of any distance dependence from the organ. Still, there is one more possibility for the couplings (one, that is novel and speculative, rather than established), namely that they reflect the entanglement between the entities. The quantum mechanical entanglement effect is distance independent, this being the basis of the Einstein-Podolsky-Rosen paradox, and its occurrence is predicated only by the different dof having been in conjunction once upon a time. This demand is undoubtedly satisfied by the zygote stage of embryonic development, from which animal organs eventually emerge.

7. Conclusions

It may be objected that an attempt to portray biological entities as microscopic systems is a futile undertaking, due to their complexities, but it should be noted

that for long decades the measurement problem in QM was treated, by von Neumann and subsequently, in a similarly abstracted form, in spite of most measurement apparatus having complexities approaching those of biological systems [56] [57]. (In a Wigner formulation of the measurement problem even the experimenter's brain (mind ?) was added to good measure, as a determinant of the physical state.) Alike to the von Neumann formulation of the measurement process, the durations of the three processes (SR, metabolism, self repair) are here left out of considerations.

Regarding the interface of the present work's methodology with the very extensive philosophical discussions on causation, in their terminology this methodology is set on a bottom-to-top approach, contrasting with the advocacy of the opposite, top-to-bottom explications, strongly argued in [58]. In this context, the title phrase "More is Different" due to the eminent physicist P.W. Anderson is sometimes cited as a call to arms for phenomenological descriptions and even the superfluousness of research at a more basic level. In fact, a proper reading of Anderson's article shows that his advocacy was for a steadfast funding of phenomenological research, conducted mainly in the sciences of condensed matter and against the mega-funding of particle physics. This was in line with the view, expressed by him at occasions, that greatly significant advances in Physics take place mainly through novel experimental results (achieved frequently thanks to refined techniques), to be followed by a careful reading of the findings by theoreticians.

In the last four decades we have witnessed numerous, perhaps thousands of intensive computational efforts to elucidate the quantum mechanical basis of specific biological structures and activities [25]. The present work is in a different direction: a formal blueprint set out in general terms. It does not reduce the need for further work of the former kind.

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Endnote Added after Acceptance

The equilibrated-quantum-states, holistic approach proposed in this paper, contrasting with the conventional non-equilibrium description of living matter's functioning, possesses an analogy with theories of electrical conduction which, after generations of being viewed by the Drude theory as a non-equlibrium phenomenon, has been superseded by a scattered quantum-state treatment (through inclusion of the leads as part of the system) in the Büttiker-Landauer-Imry theory [59].

Data Availability

The data that support the findings of this study are available from the author

upon reasonable request.

Conflicts of Interest

The author declares no conflict of interest.

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The Capacitive Coupling Modalities for Oncological Hyperthermia

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Abstract

The local-regional oncological hyperthermia has various electromagnetic methods for energy-transfer. The differences involve conceptual considerations and technical solutions. The most frequently applied energy transfer is capacitive coupling, concentrating the electric field to be the active heating component. The realization of the capacitive coupling set-up is divided into two different categories based on their goals for heating: 1) the homogeneous (conventional) heating, using isothermal conditions for dosing, and 2) the selective heterogeneous heating, using cellularly absorbed energy for dosing. The homogeneous heating utilizes plane-wave matching, absorbing the wave for energy transfer. The heterogenic heating uses impedance matching, selecting the malignant cells by their electromagnetic specialties, like their heterogenic impedance, higher membrane-raft density, and different spatio-temporal (pathologic pattern) arrangements. This article's objective is to compare and discuss the details of the two kinds of capacitive coupling techniques.

Keywords

Plane-Wave Matching, Impedance Matching, Apoptosis, DAMP, ICD, Selective Heating, Electromagnetic Heterogeneity, Membrane Raft

1. Introduction

1.1. Strategy in the Fight against Cancer

Life is based on energetically open systems, where environmental conditions determine their equilibrium. The general system's theory [1] was one of the early efforts to show the complexity of open living systems focusing on the deep embedment of its processes in the environmental interactions. Due to the environmental actions, the physical laws work well to explain the evolutionary processes

[2]. The energetically open living system intensively interacts with its environment, exchanging molecules and various thermodynamic and electromagnetic parameters. Simply speaking: our focus differs from living motility to the energy-transfer. A. Szent-Gyorgyi described the life-energy relationship using the analogy that it is not important that the monkey goes through the jungle, what is important is how the jungle goes through the monkey, in the form of nutrition, water, and oxygen, keeping the monkey alive using the environmental energy-sources [3]. The living system is complexly controlled, to maintain homeostasis. Diseases, especially cancers, break the relative equilibrium and risk the system's relative instability. The human body tries to re-establish homeostasis in many ways by enhancing the negative feedback controls. Multiple actions of human physiology try to compensate and correct the damage caused by cancer.

Healthy homeostasis struggles to control the malignancy. The first few attempts block the proliferation and start intracellularly controlling the DNA replication. It fails for various reasons, including genetic aberration [4], mitochondrial dysfunction [5], or other intracellular [6], and additionally extracellular [7] hallmarks of malignancy.

The malignancy in this general meaning is a distortion of the healthy cellular network, the rules of a multicellular organization being broken. The breaking of cellular networks is a general behavior of all tumors independent of their locations within the body. In this sense, cancer is an organizing (networking) disease, where the cells unleashed from their networks abandon the living advantages of collectivism, and individualism prevails [8]. Cancerous and bacterial proliferations have a lot in common [9]. The tumor itself has atavism qualities [10], in the sense that the malignant cells act like self-ruled unicellular organisms. The atavism-like process is general, not only with the loss of cellular connections but also with the altered intracellular genetic structures. The unicellular individualism develops the great potential for adaptability to environmental changes, making these cells more vigorous than those in the multicellular network. The modified genetic activity at the active boundary between unicellular and multicellular areas, causes disorganization of the multicellular structure, promoting primitive transcriptional programs [11]. However, the similarity with atavism is only formal. The atavistic development is supported by the environment which is rich in energy-resources needed for the proliferation. Still, the active use decreases the valuable matter around the bacteria, and only some physical processes (like diffusion, flows in aqueous solution, etc.) may passively replace the missing materials. In cancer conditions, the proliferating cell actively changes its environment, forcing the healthy host to supply the needed materials [12]. The cancer is afforded a friendly environment by the host, which tries to "heal" the abnormality by strengthening angiogenesis, injury current, and numerous other supportive mechanisms. There are telling arguments for the likening of the cancerous process to wound repair [13]. The bio-system falsely recognizes the tumor—as a wound and stimulates its environment to heal the irregularity (meaning to produce cells to heal) [14].

We are in a war against this disease [15]. The end of this war seems to be far away [16]. This war's strategic decision may be borrowed from the military: attack the enemy's weakest point, and avert to direct fight with its strongest forces. The most vital force of the malignancy is its uncontrolled proliferation, while the weakest side is the autonomy of the proliferated cells, and their isolation from the regular cellular network. The cooperation of the healthy cells regulates, controls, and supplies the members of the network. The malignant cells are "individual fighters" competing against all healthy and malignant cells for the energy sources to proliferate. This "loneliness" behavior makes the malignant cells vulnerable. They miss the complex support from the network. The missing network otherwise helps the proliferative development due to the easy motility and forming micro and macro metastases. Following this strategy, the final aim of cancer treatments is to eliminate the cancer cells throughout the body.

1.2. Some Tactical "Weapons"

To follow the strategic goal to attack the malignant cells' individualism, we have multiple "tactical" possibilities to choose from. The lack of coherence and support it in the network modifies the cells and their microenvironment. This modification could be used to select and kill the cells. The most characteristic changes are a result of the cells' autonomy:

- The individual cells are more vulnerable than the cells connected via the network. Healthy cells may share their extra absorbed energy with the neighbors, while the autonomous cells are at risk of being overloaded by the absorbed energy can be overloaded.
- The autonomy means that the cell's microenvironment is like an ocean around it, only with a few, if any, connections. The molecular "bridges" that made the bonds in the network are broken, and numerous transmembrane proteins remain unconnected and free to move along the membrane and form clusters.
- A large part of the homeostatic control is missing due to the autonomy, and the cells live unregulated. This allows the use of metabolic mechanisms which are rare in networked systems. The mitochondrial symbiosis with the cell has less importance and becomes mostly dysfunctional.
- The autonomy promotes cellular motility that uses the transport systems (lymph and blood), and once separated from the group, these cells more vulnerable.
- Consequently, the energy-demand massively increases in malignant cells as the cells require the extra energy to produce the daughter cells and to support the entire division process.
- The basic chemical reactions are out of systemic harmony. The long-range, and broadly scaled fluctuation and constant multiscale entropy is broken by autonomy, producing easily distinguishable fluctuations (noises) in measurable electromagnetic signals.

The above points are interconnected, and the "tactical actions" could affect many of them simultaneously. Some of the popularly applied treatments are as follows:

- Change the conditions by special, strict diets (like Gerson's diet), constraining the body back to the previously working equilibrium. However, in many cases, it works against the natural homeostasis; the constrained action induces new negative feedbacks from the living object. The living organism starts to fight against our constraints together with the fight against the disease itself, which unnecessarily overloads the controlling system and could lead to its collapse, causing serious side effects.
- An interesting tactic is to put out the fire with fire. This method increases the already significant metabolic rate of the malignant cells without allowing an increased delivery of the supplies. This was the original idea of hyperthermia: to locally heat the malignant tissue, and force the cells' metabolism, without allowing the replacement of the energy. This method is against the general physiological control, which is governed the blood-flow. The higher local temperature increases the blood-flow to cool-down the targeted volume. The extra blood delivers nutrients, and oxygen, so the method could easily turn in the opposite direction.
- Some proposed treatments favor fasting or supplying the body with only one kind of nutrient, like blocking carbohydrates' consumption and expecting that the limited supply will starve the malignant cells.

The above treatments do not work, mainly because the living complexity does not isolate one of the other's dynamic characters, so the action easily turns to the opposite. The general problem with these is proposed methods is that the complexity is not accounted for in the applied principles, the principles involve oversimplified mechanisms, due to the lack of complex knowledge. This problem is well formulated by a playwriter Berthold Brecht: "The aim is not to open the door to the infinite wisdom, but to circumscribe the infinite fallacy… The main reason for the poverty in science is the conceited property." [17]. The physicist Stephan Hawking formulated the same: "The greatest enemy of knowledge is not ignorance, it is an illusion of knowledge".

The dark-side of the tactical elements is the multiple quackeries distributed by social media. This approach uses the "formal knowledge" of the complexity, declaring their method as a special secret, which drives the complex processes. This could be characterized by the statement of Frederici Di Trocchio "Swindle was used to art. Nowadays, it became a science too…" [18].

1.3. Oncological Hyperthermia

Hyperthermia in oncology appeared in ancient medicine. Today heating processes for medical purposes have become a vital "home remedy", from the sun-bathing to the hot-bathes, including the Japanese high-temperature bath and Finish sauna. Hippocrates first described the application of heat in oncology

in European medicine. The use of heat therapy to cure cancer has since emerged in various settings in the medical field. The appearance of electromagnetism in medicine renewed the heating efforts, and extended the applications for various cancers. Two main categories divide the electromagnetic-based heating applications: the local deep heating which results in local-regional hyperthermia (LRHT), and the whole-body hyperthermia (WBH). Just as the categories of chemotherapy and radiotherapy include many different modes of treatments, "hyperthermia" is also a large category with different technical aspects. Figure 1 maps the main differences between the technical solutions.

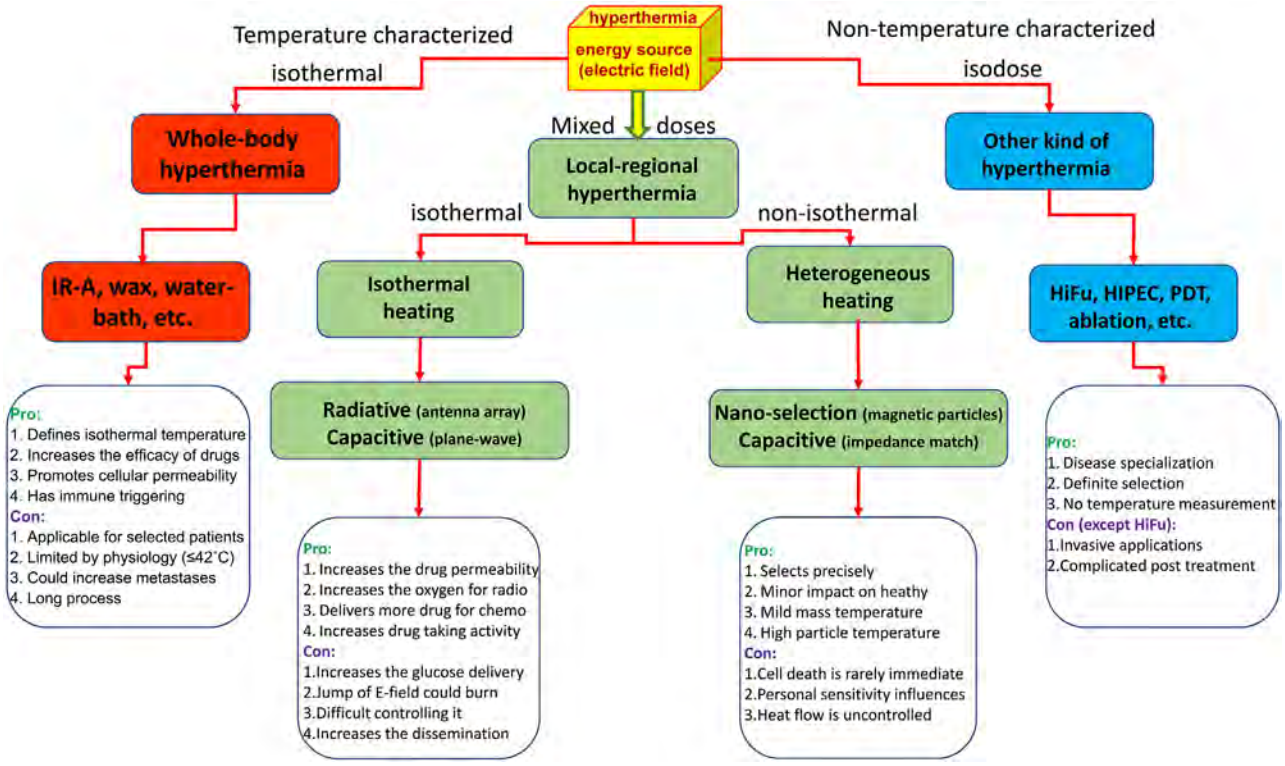

Figure 1. The major categories of hyperthermia methods.

The relatively simple physical-physiological heating concepts do not mean a simple application in humans. The complexity of human physiology, and the non-linear feedbacks of the homeostatic regulation, limits the heating possibilities. Despite the proven *in vitro* benefits of heating in cancer treatment, the clinical results have strongly demonstrated how the control of treatment is often influenced more by the human body than by the treatment intention. This complication made the development of oncologic hyperthermia non-monotonic, having both great successes and failures [19]. It was clear from the beginning of oncological applications that the real, local cell-distortion must have a high temperature, higher than the physiological limit of 42˚C. However, this limit restricts the high temperature application of WBH which has moved towards mild temperature range, promoting the reactivation of the immune system. Contrary to WBH, LRHT does not limit by the temperature in the tumor. When the high

temperature targets the healthy host tissues around the tumor, it could produce unintended necrotic burns with serious damage to the treated organ's function.

Consequently, the energy absorption during the heating process significantly depends on the technique applied. No unified protocol for the various technologically determined targets of the heat has currently been described.

The category "hyperthermia" includes various energy-absorption methods, and each individual solution requires its own protocol. It is very similar in this regard to the chemo-variants of oncological therapies. Chemotherapy, depending on the targets of the drug, has different protocols. Mixing these could cause serious adverse effects and even fatal events such as poisoning. Homogeneous targeting in most of these therapies requires very different protocols to the local or cell-sensitive selection. For example, chemotherapy is administered intravenously (i.v.), at different doses to the doses administered with chemoembolization or other types of local administration. Isodose homogeneity, as in radiotherapy, is also not used in most brachytherapies, radiation seed, or nanoparticle administration. We are sure that the hyperthermia variants also have specific differences in their dose and protocol, sharply depending on their technical solution and targeting method. Defining a general dose and protocol for all hyperthermia methods is a misleading request. The methods are not equal. Their effects are different, so the dose and protocol have to fit the specific situation.

The heating techniques determine the result of the clinical treatment. Just as the categories of chemotherapy or radiotherapy, which include many different treatments, "hyperthermia" is also a large category with different technical aspects. We have seen that exposing the tumor to 42˚C in whole-body hyperthermia has entirely different results than the same temperature in any local treatment. Characterization of the temperature alone is not enough to categorize the technical solutions.

A water bath is used in many experimental models to achieve hyperthermia, and this models homogeneous heating solutions. The various electromagnetic heating technologies also have their specialties. The bioelectromagnetic action of the technology determines the actions. Evaluating the applied technique, we consider the kind of energy delivery, the method of heat absorption, and handling the target tumor's physiological reactions, together with their inhomogeneities. The target's absorbed energy, and its temperature distribution are not the same [20], and these characteristics are largely determined by the blood-flow. The technical solutions must handle how the provided energy I transformed into the desired temperature.

1.4. The Electromagnetic Coupling Modalities

Variants of energy-transfer realize the absorption in the target. Various "antennas" (sources) couple the energy to the target (**Figure 2**). The homogeneity of the absorption defines the main character of the actual coupling. The inductive arrangements have two heating forms. One is the Eddy-current (induced current loop in the body) and the other uses magnetic materials for heating. In living

objects, both the Eddy-current and magnetic approaches are applied. Life does not have natural inherent magnetic properties. Artificial magnetic materials (like nanoparticles, seeds, rods, etc.) orient the energy for heating. Internal Eddy-current induction needs an extra high magnetic field, and the induced current has no specified orientation but is sensitive for inhomogeneities inside the body. Consequently, both induction methods heat in a heterogenic way. The conventional relative antenna solution radiates the electromagnetic energy, which is absorbed by the target. It is less sensitive to heterogenic structures, so is usually applied for homogeneous heating to use the dosing of isothermal volumes. The capacitive coupling has two major kinds of energy transfers: 1) the plane-wave antenna process, which aims to achieve similar isothermal absorption of the electromagnetic waves as the radiative applications; 2) the impedance coupling process, which uses the precise impedance-matching of the target. The isothermal kind of capacitive coupling requires high energy transferred via the plane-wave, while the impedance matching (mimics the galvanic match), uses less energy provided the heterogenic absorption processes are exploited and dominate. The galvanic coupling firmly touches the actual target. In non-living applications, this is the simple discrete resistor situation. The galvanic coupling in the case of living items applies tightly connected electrodes invasively with direct solid contact with the body's surface.

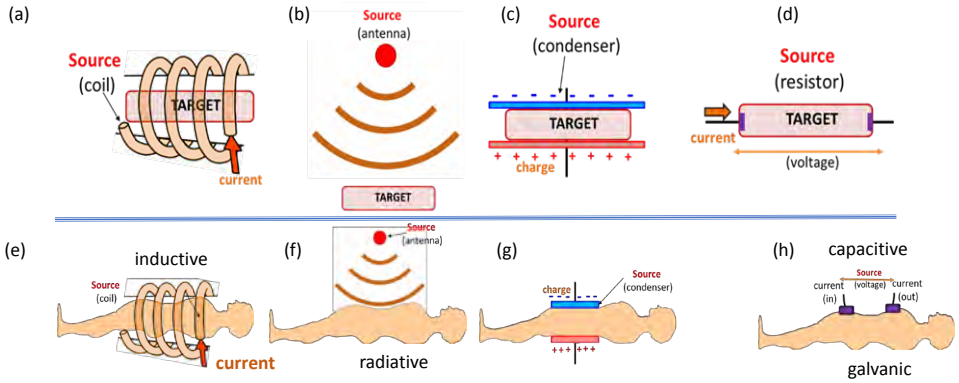

Figure 2. The major coupling methods for local-regional heating. (a)-(d) Homogeneous (non-living) targets; (e)-(h) Heterogeneous (living) target. The energy-absorption induces different effect in various couplings.

Applications using capacitive and radiative (microwave) solutions are the most popular methods used in the technical realization of the treatments; however, due to the sharp decrease of penetration depth with the increase of frequency, microwave solutions are mainly applied for surface lesions (see later). Capacitive coupling of energy delivery has become the most frequently applied technique, and the frequency of choice for the technique is the so-called "free-frequency" of 13.56 MHz, approved for industrial, scientific, and medical use (ISM frequency) [21]. Different effects in the human applications are observed, based on the coupling effects of the applied technique, **Figure 3**.

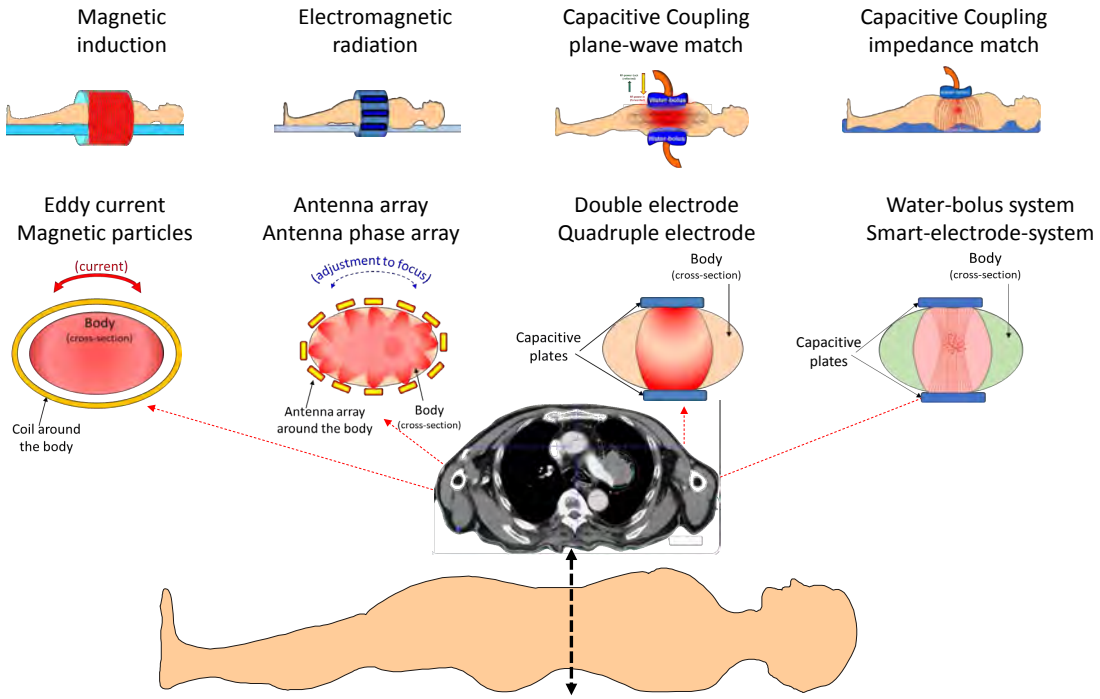

Figure 3. The local-regional treatment intends to select the cross-section of the body for energy absorption.

2. The Capacitive Coupling

Two kinds of capacitive couplings exist, depending on how the matching tunes the antenna, how the antenna structure's method and the electronical environment incorporates the tumor in the body as part of the regulated electric circuit. The concept of the complete electric circuit defines the matching method. The complete system, not only the capacitive arrangement of the electrodes, defines the coupling.

2.1. Plane-Wave Matching

The conventional solution involves plane-wave matching, in which the antenna's plane-parallel plates are tuned as per the standard antenna-tuning method. This solution does not consider the energy losses by various electric circuit elements and their interactions with the environment. In this case, the increased power (P) compensates for the lost energy. Due to the relatively high complex impedance, the voltage (V) is high, while the current (I) is low. The product of voltage and current defines the useful power, $P_{real} = V \cdot I \cdot \cos(\varphi)$, while the reactance (the power refused by the load) is $P_{react} = V \cdot I \cdot \sin(\varphi)$. The possible timing delay of the complex fit of the voltage with current is characterized by the cosine of the phase angle ($\cos(\varphi)$) of the complex values. In case of dielectric losses and/or radiations $0 < \varphi < 90^{\circ}$. Due to the losses, the impedance of the system (Z_{sys}) from the radiofrequency (RF) source to the target is large. The capacitance (C) describes the dielectric (isolating) resistivity, and the conductive part (defined by the real resistivity (R) defines the reaction time of the system (time-constant,

$\tau = R \cdot C$). The circuit for the hyperthermia plane-wave system has many various capacitances and resistivities additional to the target in the human body, and then we have to calculate the time-constant in a more complicated way (open-circuit time constant method [22]).

The time constant, in the case of plane wave solution, is relatively high, limiting the tuning's reaction time. This delay could cause a challenge when the physiological changes (breathing, heart-rate, etc.) are quicker than the reaction time. The plane wave method applies conventional antenna tuning where the antenna is fixed, so the reaction time has no relevance.

The plane-wave matching radiates RF-waves for energy-absorption, and direct heating, and necrotic cell-death (CEM 43˚C T_x dose) is expected. This matching technology aims to reach at least 43˚C temperature in the T_x effective percentages of the temperature measurement in the tumor.

The wave matching induces extensive radiation, due to the wave-transmission adding a significant factor to the energy-loss, and this could produce safety issues for operating staff. An important phenomenon of this coupling is that it could tune on the air without a patient in the active radiation zone.

2.2. Impedance Matching

The impedance matching of capacitive coupling does not use the wave concept. The system construction approaches the galvanic touch of the electrodes. The normal resistor has the maximal power in the galvanic coupling: $P_{\max} = U \cdot I$, where U is the galvanic potential (voltage), and I is the current (Amps). In the case of a patient's complex impedance (Z_{pat}) the imaginary part limits the effective power. When Z_{pat} coupled galvanically, it modifies the maximal efficient power to: $P_{Pat} = U \cdot I \cdot \cos(\varphi)$. A resonance solution of the components approaches the minimal imaginary part of the Z_{pat} impedance [23], and maximizes the power on the patient. The resonance uses a near-zero phase angle $\varphi \cong 0$ consequently $\cos(\varphi) \cong 1$ [24]. The low imaginary part decreases the voltage and increases on the same ratio the RF-current, [25] [26]; because $I_{Pat}^2 = \frac{P_{Pat}}{Z_{pat}}$, and $U_{Pat}^2 = P_{Pat} \cdot Z_{pat}$.

Approaching the proper impedance matching, the solution has negligible reflected power (order of 1 W), mimicking the skin's galvanic contact as much as possible. When the electrodes directly touch the targeted volume's surface, the galvanic situation, without any isolating materials, offers the most amount of available current. The impedance matching aims to mimic the galvanic situation as much as possible. This solution minimizes the reactive part and maximizes the real power on the load.

The main principle of impedance matching is to approach the "galvanic-like-touching" that would be the best available non-invasive electromagnetic energy-delivery. The invasive method (when electrodes are inserted into the body) is also "galvanic", but its invasivity has multiple medical complications,

such as bleeding, a high risk of infections, ulcer formation, and inflammation. One of the invasive "galvanic" methods is ablation technology, which has remarkable successes in local, small tumors [27]. With minimal energy loss, impedance matching allows the concentration of the energy on the malignant volume [28]. Due to the selection, this solution has better efficacy and offers a safer treatment because the voltage could be less than in higher resistivity isolation cases, at the same power application, while the current is increased.

The full arrangement of impedance matching minimizes the losses in the circuit ($Z_{loss} = Z_{sys} - Z_{pat} \Rightarrow min.$). The minimal loss allows optimization of the reaction time with a low time-constant. The small delay of the reaction to the physiological changes allows prompt adaptation to alterations during the treatment; even small animals in preclinical experiments have a significantly higher heartbeat and breathing frequency than humans [29].

The impedance matching needs a conductive media between the electrodes, and the RF-current flows through it. Consequently, the system cannot tune on the situation when a patient does not present in the active radiation zone. The technique therefore induces minimal radiation to the environment, and it is safe.

Due to the forced RF-current, the patient becomes an electric component of the real-time adaptive tuned electric circuit, representing active electrical impedance. In this matching, the patient is not simply an "energy absorbent" but an active electric element of the serial circuit.

2.3. Comparison of Capacitive Couplings

In general, all capacitive couplings are equal based on the formal capacitive arrangement level, however their technical details differentiate them. The variation could be so significant that it produces—either homogeneous or heterogeneous heating in the target.

Comparing the variants of capacitive couplings requires a detailed study of the electronic, structural, and material design differences of the circuits. All capacitive couplings involve a capacitor used for energy transmission to the target, emphasizing the electromagnetic interactions' electric field component, using electrodes with the target volume placed between them.

The plane wave capacitive coupling transmits the radiofrequency by the plane antenna, and some of the radiofrequency is even transmitted through the air, **Figure 4**. A popular hyperthermia technique applies a typical radiative plane-wave solution [30], but the high voltage for radiation necessitates enormous power (600 W for a mouse with tumors weighing 2 g) [31] [32]. However, the plane-wave solution could work with a lower power when the distance (space in the air) between the electrode and the body surface is small, or negligible, or the matching parameters allow high voltage and low current for the applied power.

Importantly, impedance matching of capacitive coupling does not work when isolated (*i.e.* when there is a space or air between the electrode and body surface), **Figure 5**.

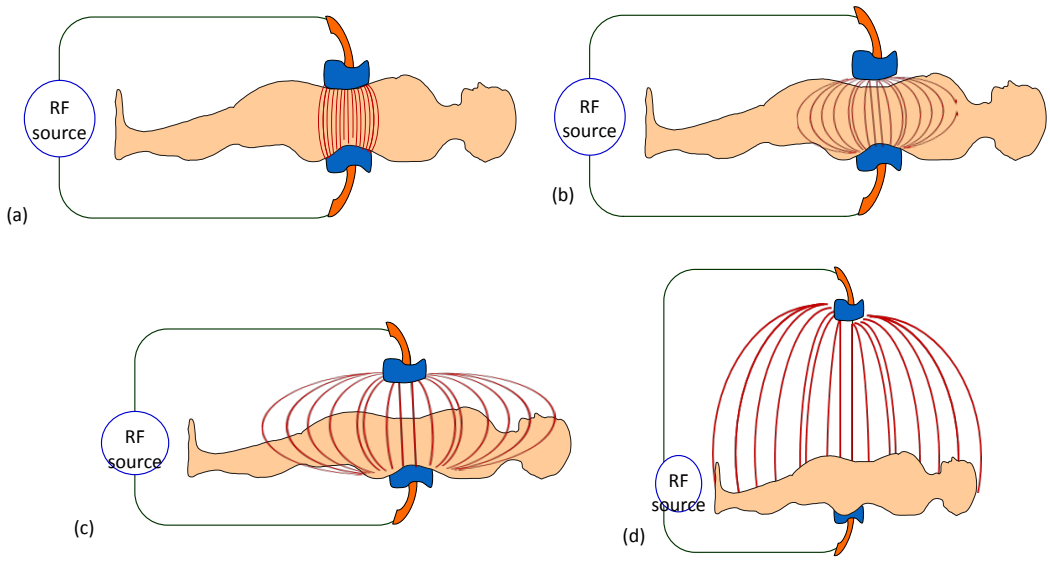

Figure 4. The plane-wave radiation works through the air, and so it is not sensitive for electrode fixing.

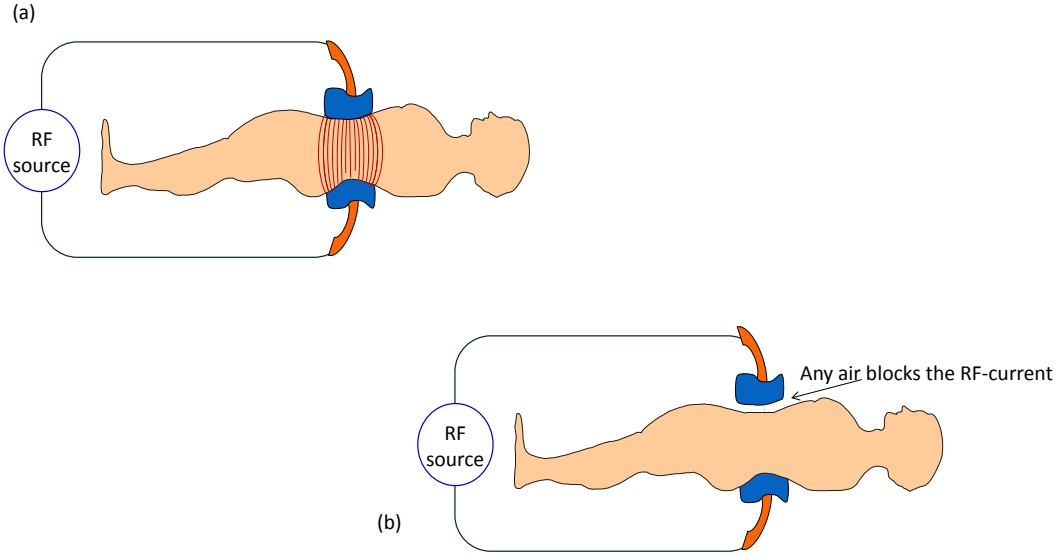

Figure 5. The impedance matching uses the RF-current-flow through the body and does not work when an air slit exists between the electrode and the body.

All capacitive couplings have an engineering control point to optimize and maximize the provided power from the RF source and, using the power-supply safely, to avoid its overheating. The measuring points fit the circuit's impedance to the source's internal resistivity, using the conventional standard 50 Ω. However, this engineering control does not take into account the medical control. The medical control or reference point refers to the point at which there is minimal loss of energy to the environment and maximal absorption in the patient while ensuring the safety of the patient and minimizing unwanted hot spots.

The optimal engineering settings do not necessarily align with the optimal requirements for the patient safety and treatment, **Figure 6**.

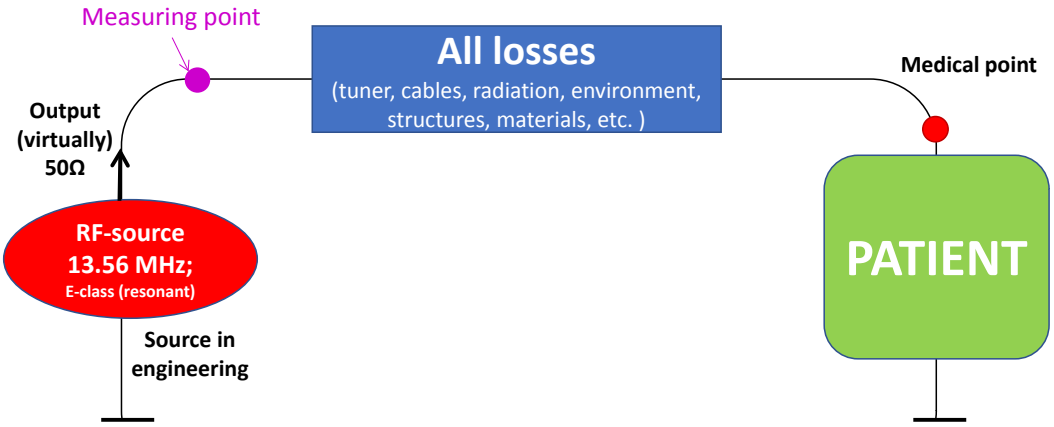

Figure 6. All losses are minimized by proper geometry, material-selection, careful design of specialized electronics, super-low imaginary (reflected) power, ($\varphi \cong 0$) etc.

There are decisional differences between the realization of capacitive coupling methods at the level of simple measuring observations. The two major categories are the plane-wave and impedance matching techniques **Figure 7**, and other solutions combine these two categories.

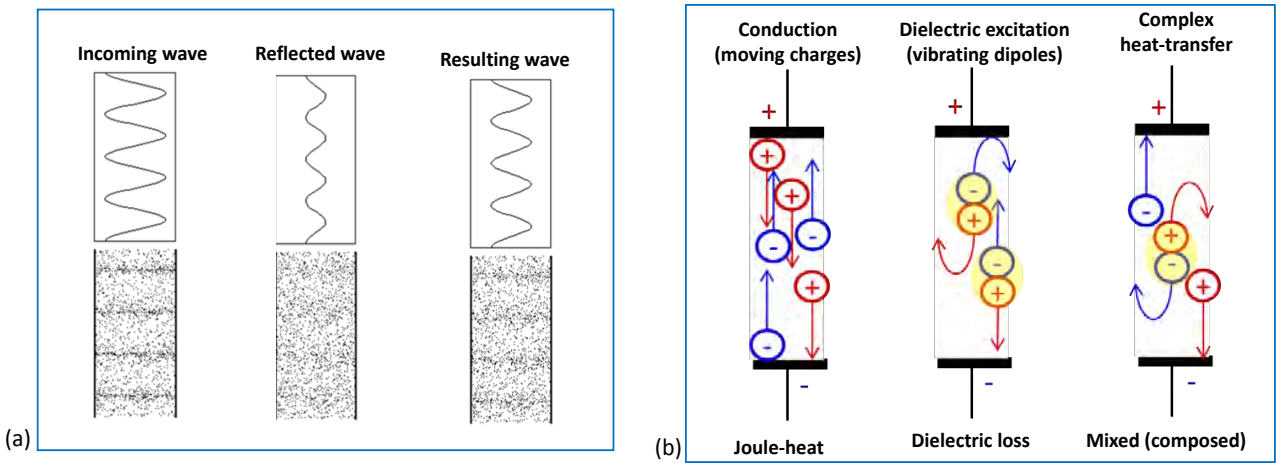

Figure 7. The matching arrangements. (a) The plane-wave matching uses a forwarded power and measures the reflected one to deduct and calculate the resulting radiative power; (b) The impedance (quasi-galvanic) matching uses the current-flow of the free charges (ionic species in aqueous electrolytes in the body) and the rotational or gradient-induced linear movements of dipoles in the tissues.

The observed differences could be technically detected by measuring the engineering reference point (optimal engineering set-up), and the medical reference-request point. The inequality between the reference points is due to the losses in the circuit, including the matching tuner, cables, radiation processes, used materials, and structures, as well as the capacitive coupling with the environmental objects (like walls, other types of equipment nearby, or the operating personnel). At this point, the engineering control and the medical control could significantly differ from each other, **Figure 8**.

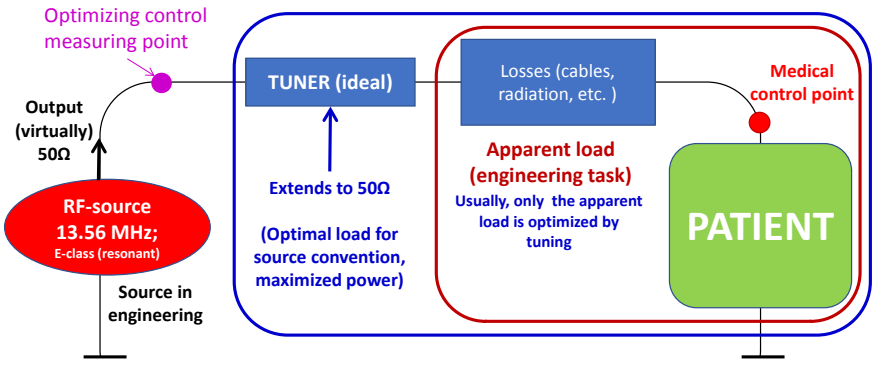

Figure 8. All losses are minimized by proper geometry, material-selection, careful design of specialized electronics, super-low imaginary (reflected) power, ($\varphi \cong 0$) etc. The matching has to accurately control the medical point shown in the figure.

The tuner electronically compensates for the overall losses, and the power-supply increases the power to replace the missing, lost energy. This type of matching procedure favors plane-waves on the patient, which uses wave-absorption, with a particular exponential decrease from the surface incident energy in the body, and is intended to create homogeneous heating in an actual depth.

The compensation of the general losses by the circuit components and environmental interactions do not optimize the patient-power from a medical point of view. After the medical point (which begins at the electrode), the initial RF-current enters the "coupling complex," including the patient's targeted volume. After this point, new unwanted losses challenge the optimization of the treatment. These include the electrode structure, electrode material, the bolus system, the patient's surface adipose tissue, the healthy impedance, etc. This extra impedance is the vital target: the impedance of the tumor. Hence the optimization of the treatment point is crucial in order to successfully heat the tumor. How this is optimised defines the type of capacitive coupling (**Figure 9**).

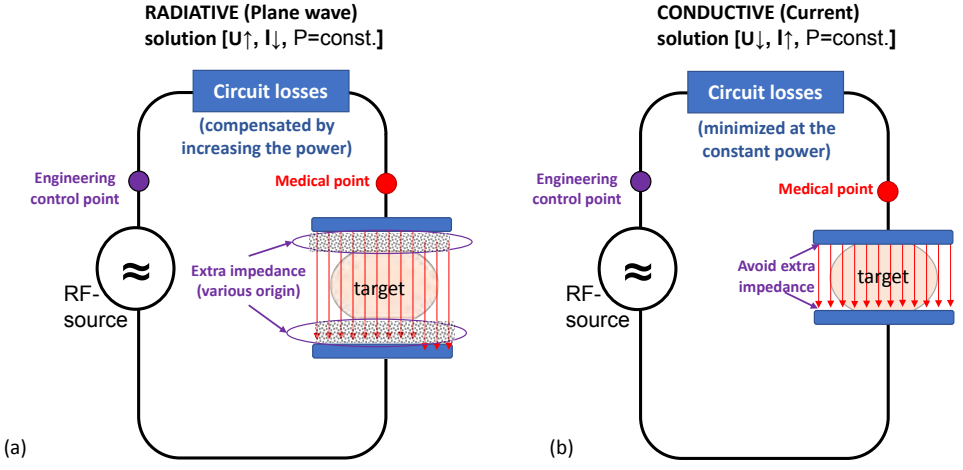

Figure 9. (a) The plane-wave matching allows a lazy connection of the electrode for various reasons; (b) The impedance (quasi-galvanic) matching does not work with improper impedance between the "medical point" and the body surface.

The impedance matching focuses on the medical control-point, minimizing the impedance of components that derail the primary target's energy, the tumor. Without taking into account the medical point, the RF-current flows through two different impedance categories: the objects' impedance, which fits the current transfer to the body, and the body impedance.

The various components of object impedance challenge the conductive approach (Figure 10).

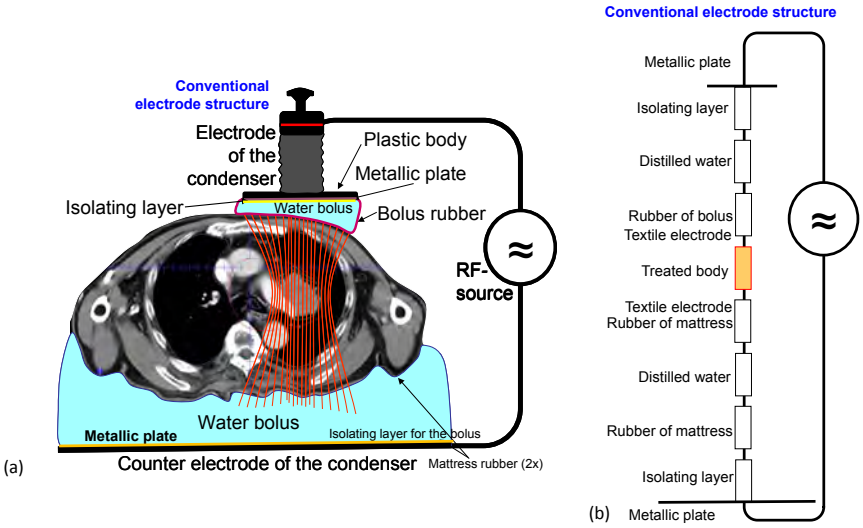

Figure 10. Numerous serial impedances modify the energy-distribution in capacitive coupling. (a) The main structure of the conventional capacitive coupling with water-bolus; (b) The draft of the impedance of the conventional electrode structure.

The best solution would be the galvanic contact of electrodes (Figure 11), which may be approached by the electrode design accompanied with the resonant compensation.

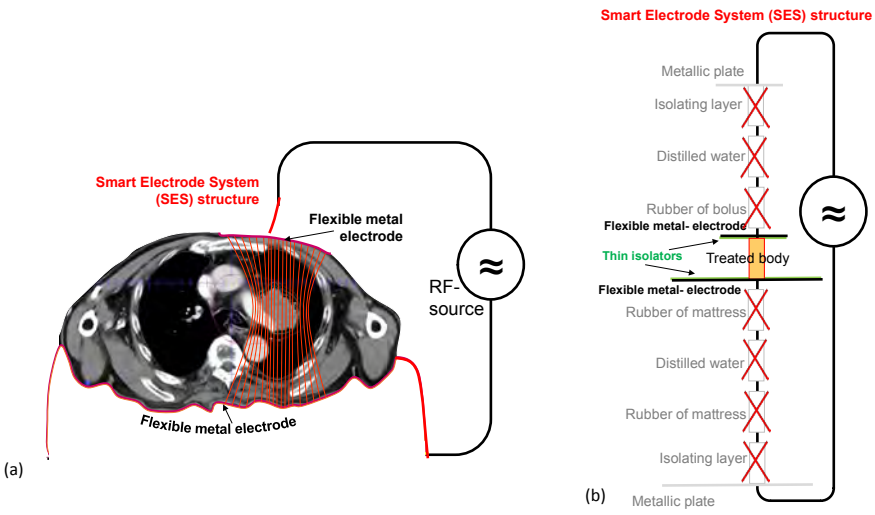

Figure 11. The draft of the design of impedance matching, which is (a) quasi-galvanic, or (b) the solution mimics the galvanic touching with a precise resonant compensation.

The body impedance contains a very heterogenic structure. Each of which represents a resistor and a serial capacitor (the inductive parts are missing) (Figure 12).

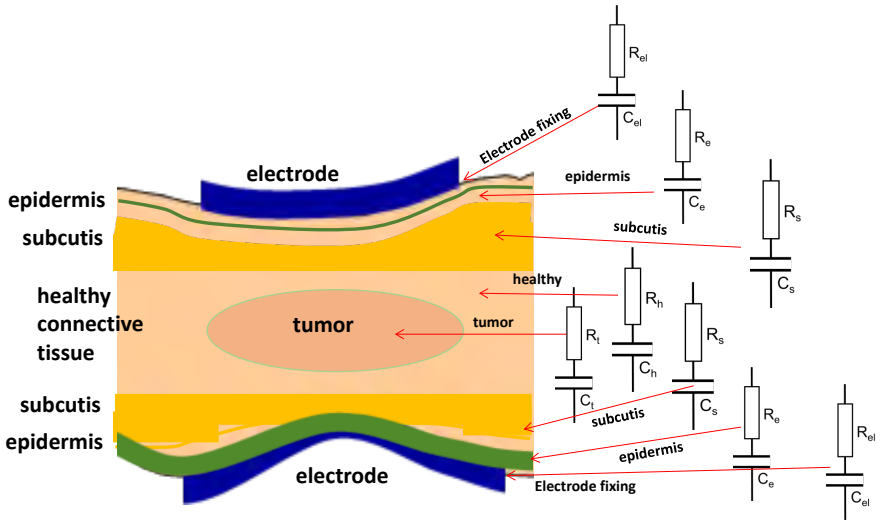

Figure 12. The major layers of the human body's targeted volume show the serial RC parts in every layer.

The compensation procedure in impedance matching minimizes the capacitive (imaginary reactance) factor, and the resistive part remains in focus. A particular category of impedance matching is the modulated electro-hyperthermia (mEHT) which selects the malignant cells in this heterogeneity, and the tumor-cells concentrate the primary energy absorption (see later text below). Consequently, the dominant resistivity part is the set of the tumor-cells in the targeted volume. On this basis, we approximate the effect of the different resistivities and the resistivity of the healthy tissues is negligible in the first attempt (Figure 13).

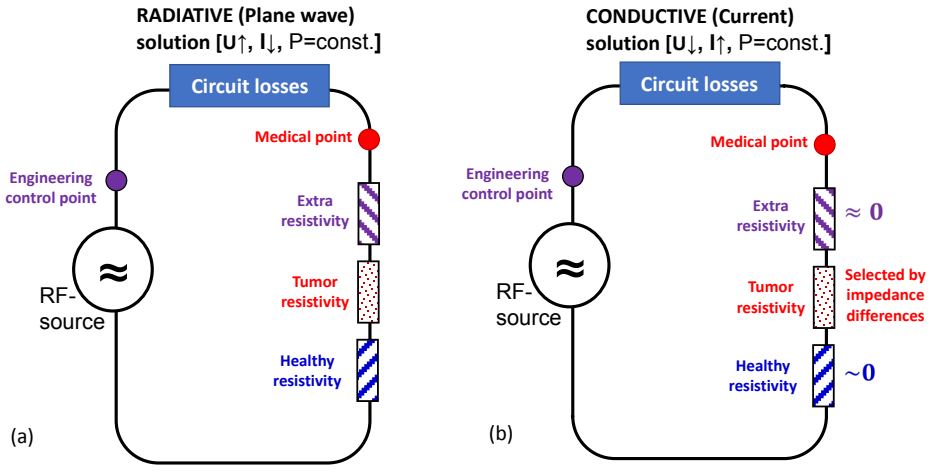

Figure 13. The voltage and current generation with the same value of power in plane-wave matching (a), and in impedance (quasi-galvanic) matching solutions (b).

All of these considerations involve a resonant matching method. AC/RF circuits imply a certain frequency determined by the values of the resistance, capacitance, and inductance of the serial circuit (Figure 14).

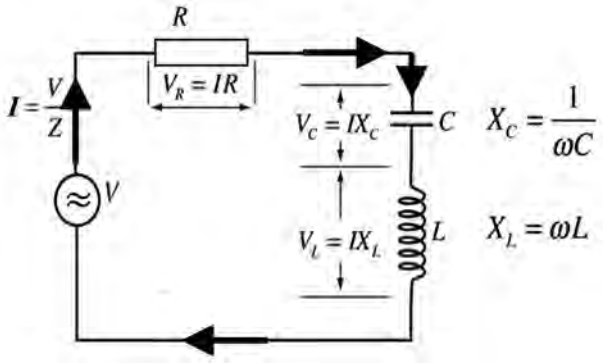

Figure 14. The discrete representation of the circuit describing the impedance matching. V_R, V_C and V_L are the voltage drop on the discrete elements. The resonant compensation produces the V_L.

The dielectric permittivity and the conductivity affect the RF-current differently, and the result is called impedance. Mathematics using complex numbers describe the two independent effects showing the conduction on the real conductor while the dielectric permittivity defines the isolators, where the conduction of the RF-current is imaginary. The patient's impedance represents the real part (R_{pat}), and the reactive part (Y_{pat}), and $Z_{pat} = R_{pat} + iY_{pat}$, where $i = \sqrt{-1}$ denotes the imaginary part. In geometrical representation, it shows a vector (Figure 15).

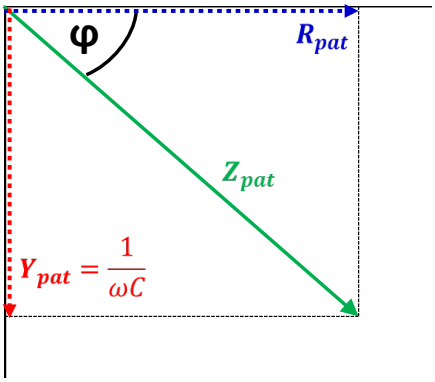

Figure 15. The vector picture of the impedance in living objects. The R_{pat} real resistance and Y_{pat} imaginary reactance produces the Z_{pat} impedance with the φ phase angle. Due to the only capacitive part (no inductive element exists in the living organisms), reactance is negative. The current appears earlier on the capacitor than the voltage. The impedance matching approaches the $\varphi \cong 0$ compensation.

The impedance minimum characterizes the serial resonance. The impedance from the imaginary parts of capacity (C), and inductivity (L) are $Y_C = \frac{1}{\omega C}$, and

$Y_L = \omega L$, respectively, and the impedance is $Z = \sqrt{R^2 + (Y_L - Y_C)^2}$. Hence, when $\omega_0 = \frac{1}{\sqrt{L \cdot C}}$ then $Y_L = Y_C$, and the resulting minimal impedance is $Z = R$ with zero phases. The selectivity of a circuit depends on the circuit's serial resistance.

The Y_{pat} depends on the applied frequency (f), while the real conductor does not depend on f. The living matter has a negligible inductive (coil-like) component in Y_{pat}. Mostly the membranes, and the other isolation layers form Y_{pat}, which act as a C capacitor, $Y_{pat} = \frac{1}{2\pi f C} = \frac{1}{\omega C}$ Where $\omega = 2\pi f$. Applying the vector representation of the impedances (Figure 15), the variation of the major layers in the target volume of a human body gives a resultant impedance $R_{pat} = \sum_{i=1}^{N} R_i$, and $Y_{pat} = \frac{1}{\omega} \sum_{i=1}^{N} \frac{1}{C_i}$. Using the resonance frequency $\omega_0 = \frac{1}{\sqrt{L \cdot C}}$, an additional inductive factor would compensate the Y_{pat} to minimize the impedance of the target. The necessary inductivity for resonance is $L = \frac{\omega_0^2}{C} = \omega_0^2 \sum_{i=1}^{N} \frac{1}{C_i}$ (Figure 16).

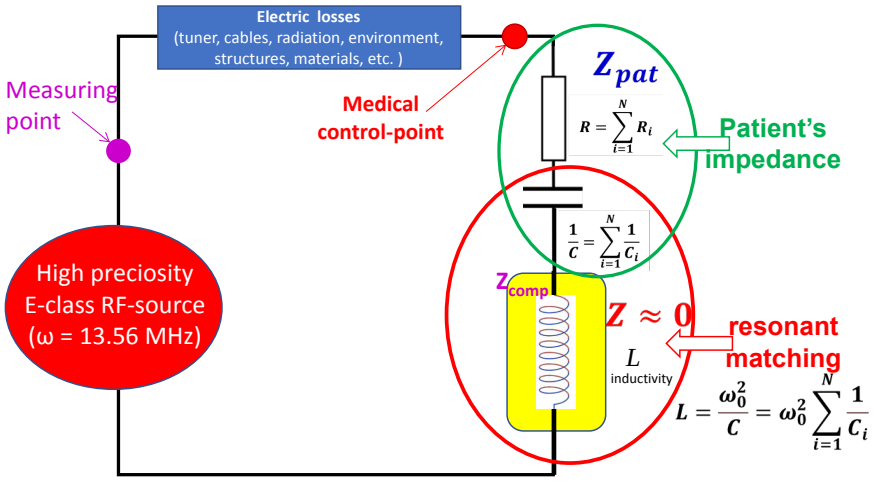

Figure 16. The patient is an electric component of a precisely tuned resonant circuit. The compensation clears the target impedance minimizing its reactance.

The compensation transforms the impedance near a real resistance value as shown in vectorial representation (Figure 17). The vectors show the complex impedances of some critical layers in the body during the RF-current flow. The horizontal axis is the real part (the real conduction), while the perpendicular one is the imaginary part, representing the isolation. All tissues have isolation also due to the various membranes. The electrode isolations are neglected, so the resulting impedance vector shows a decline, which a single inductive resonance could easily compensate for.

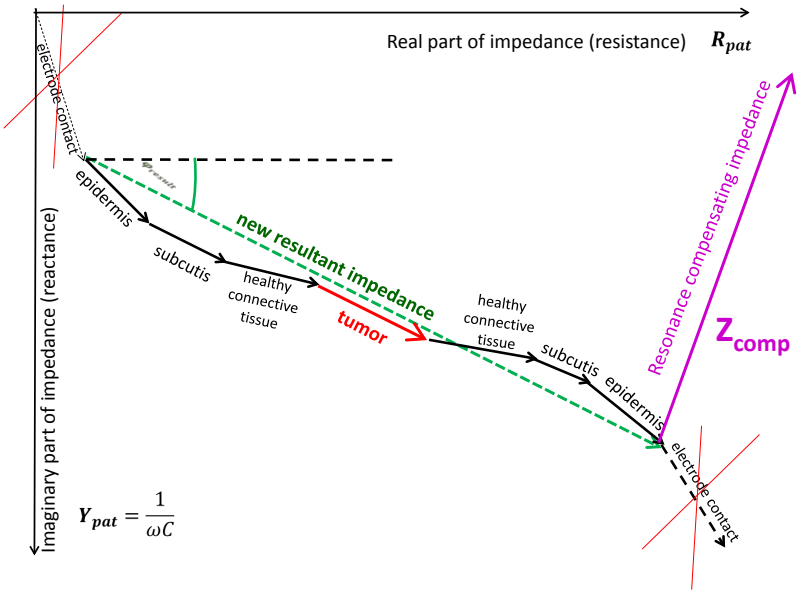

Figure 17. The vector diagram of the cross-sectional impedances in the average human body. Only the major components are shown, and for clarity, they are regarded as a discrete element.

The original current was $I_{orig} = \frac{V}{Z} = \frac{V}{\sqrt{R^2 + \left(\omega L - \frac{1}{\omega C}\right)^2}}$, the new current in resonance is higher $I_{orig} < I_{res} = \frac{V}{R}$, and in resonance depends only on the real resistivity. The current changes by resonance. The RF-current flowing through the target depends on the values of the components of the circuit. The well-selected situation filters a relatively small part of the targeted volume, the malignant cells, so their resistivity is small compared to the complete targeted volume. The small resistivity increases the peak of the current in resonance, **Figure 18**.

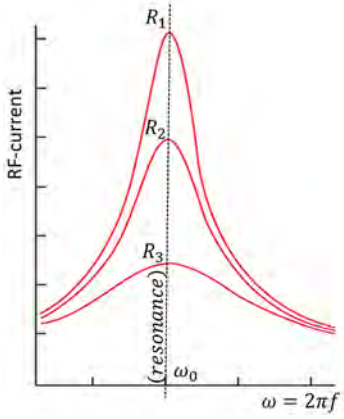

Figure 18. The RF-current distribution in the resonant conditions. The resistivity is decisional; when it is low, the peak is sharper ($R_1 < R_2 < R_3$). The $f_0 = \frac{\omega_0}{2\pi}$ is the resonant frequency.

Since this power depends on the square of the current the resonant curves appear steeper and narrower in the presence of lower resistivity. The quality factor Q is defined by $Q = \frac{\omega_0}{\Delta\omega}$ where $\Delta\omega$ is the width of the resonant power curve at half maximum (Figure 19).

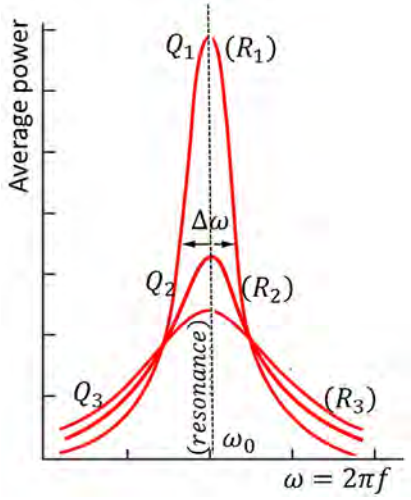

Figure 19. The resonance quality factor (Q) defines the average power in resonance. $R_1 < R_2 < R_3$, and so $Q_1 > Q_2 > Q_3$. The $f_0 = \frac{\omega_0}{2\pi}$ is the resonant frequency.

Since that width turns out to be $\Delta\omega = \frac{R}{L}$, the value of Q can also be expressed as $Q = \frac{\omega_0 L}{R}$. The Q is a commonly used parameter in electronics, with values are usually in the range of Q = 10 to Q = 100 for circuit applications. The smaller the resistance, the higher the "Q" for given values of L and C. The power, of course, depends on the product of actual current and voltage. When the current increases due to the resonance, the voltage decreases, while maintaining the same power.

The resonant approach uses the minimizing of the reactance (imaginary part) of impedance. Physiological regulation also has a vital role in the process. One of the reasons for using the plane-wave capacitive coupling is the surface adipose tissue challenge, forming an isolator-like layer at the skin. In a plane-wave situation, the voltage is increased to surmount the gap by the isolator of the adipose layer. However, this way, the energy-absorption in this layer is extremely large, so the risk of burn increases. In order to avoid this risk, the plane-wave method uses intensive cooling of the skin by using the bolus system, Figure 20.

However, this cooling has unexpected positive feedback reactions from the physiological control of the body homeostasis: the cooled skin lowers the blood-flow in the subcutis, which increases the layer's isolation towards RF-current. This induces a higher voltage request, which increases the risk of burn, so a further increase of the cooling is necessary. It further increases the isolation, and so

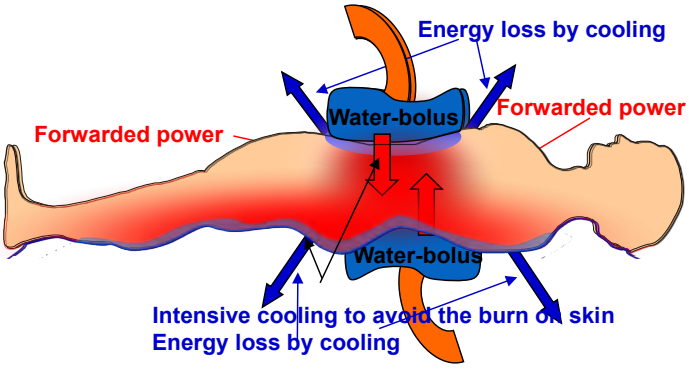

Figure 20. The cooling of the bolus produces uncontrolled energy-loss and induces a positive-feedback physiological regulation. (see the text)

on, the situation would be hard to control. Furthermore, the intensive cooling absorbs a large part of unmeasured energy, which makes the therapy dosing with incident energy impossible, as is similar in the case of ionizing radiation. Consequently, the impedance matching takes attention to the cooling process and keeps the homeostatic control stable in the subcutis layer under the electrodes.

In summary, the strategy of impedance matching concentrates on increasing the current as much as possible. The major factors to maximize the current are:

- the resonance approach,
- the design, structure, materials of the electrode system,
- the grounding optimization to lower the radiation, and coupling to environmental objects,
- the regulation of the homeostatic status of the skin blood-flow (which regulates the imaginary part of the skin-structure of the patient),
- eliminating the losses in an electric circuit as much as possible,
- the high current value (in the unchanged power conditions) makes a more effective selection,
- the high current accompanied with low voltage at the constant power, increasing the safety of the treatment.

3. The Modulated Electrohyperthermia (mEHT)

3.1. The Challenge of Homogeneous Heating

The classical heating concept applies a mass-heating of the entire tumor. The mass heating tries to be homogeneous in temperature (isotherm), and uses the temperature as the only control parameter.

The control of homogeneous (conventional) heating is problematic because

1) the local blood-flow is enhanced, which increases the risk of dissemination and metastases,

2) colossal power is necessary to ensure quasi homogeneity, which again involves many safety issues,

3) due to the heterogeneity of the target, the control of homogeneity is very complicated, in most cases it could not be achieved,

4) the homogeneous hyperthermia thermally kills the cells and occasionally triggers immunogenic effects in the area,

5) the challenge of measuring temperatures at has not been solved; MRI thermometry is promising but still has challenges,

6) the only homogenous (and large CEM43T100) solution is the whole body treatment (WBH), which does not show the expected success.

The invasive measurement of the tumor's temperature has multiple problems, as a result the temperature is typically measured in the nearby lumina or cavities of the body. So the mass heating must be regional, having comparable temperature in the nearby lumen (like oesophagus, bronchus, colon, vagina). The same isotherm heating appears in the plane-wave concept of capacitive coupling. The modulated electro-hyperthermia (mEHT) method uses impedance matching of capacitive coupling with some unique features, which have been developed over the past 32 years, and documented and patented. The mEHT method harnesses the impedance matching shown above with additional elements, improving its efficacy.

The present technical challenges are:

1) The energy selection ensures the local place of energy absorption. It has major complications due to the normal physiological movements caused by breathing; and the technical solution has limitations when attempting to heat deep-seated tumors without considerable heating of other tissues.

2) The dose determination, which controls the medical application, is a mandatory parameter, but the heating techniques determine the clinical results. We have seen that exposing the tumor isothermally to 42˚C in whole-body hyperthermia, has entirely different results than the same temperature in any local treatment. The technical solutions based on the temperature alone do not characterize the applied method.

3) The role and measurement of temperature in the treatment efficacy are challenging. The value of the temperature in the target supposes an isothermal mass-heating, which never happens in LRHT. The temperature measurement approximates the tumor's value, checking the temperature in the nearby lumen (like esophagus, bronchus, colon, vagina). This method assumes that the heating does not focus on the tumor-mass, but equally heats its healthy environment.

Due to the above challenges, temperature measurement is mandatory to approximate the absorbed energy, which differs from the technically provided value. The high energy losses (like various electric losses, losses from cooling water, etc.), and the need to control safety (avoid burns) are fundamental reasons to measure the temperature.

3.2. Heterogeneous Heating

The mEHT chooses a new paradigm, it heats the cancer-cells selectively in the tumor, using the malignant cells' unique thermal and electromagnetic characteristics. The structural change of the local heat-capacities, heat-conduction differences, heat transfer by blood, and lymph electrolytes cause the thermal hete-

rogeneity. Significant differences in the electric behavior of micro-states of living matter determine the electromagnetic heterogeneity. The variation of electric conductivity and dielectric permittivity by the living processes and the differences of lipid-protein structures in the cell-membranes and the cells' cooperative differences appear to be the most influential factors for electric heterogeneity. Further differences between the malignant cells and their healthy counterparts develop as a result of the heat-resistance, motility of the cells, and cellular and extracellular mechanical properties.

Some other significant differences are present at a molecular level, but these are less effective in distinguishing the malignant cells from their healthy counterparts. Using heterogeneity offers a valuable tool to select the malignant cells in the heterogenic tissue. The RF-current presents a possible tool for clear recognizing of the heterogeneities. The current-flow changes based on the electric heterogeneities and its heating effects connect the current to the thermal properties. An essential component of tissue heterogeneity involves molecular reactions, which differ depending on the tissue and cells. For example, the apoptotic control, a well-known regulation in healthy tissues, is almost entirely missing in malignant tissue, as described in the hallmarks of apoptosis could happen through multiple molecular mechanisms, which do not work in cancer.

3.3. Considering the Homeostatic Regulation

From the beginning of human medicine, physicians recognized the equilibrium of the living organisms, which defines the healthy state, and has multiple dynamic components which are finely balanced. This was the first recognition of homeostasis, which has definite lower and upper limits of the interactions and conditions. The body homeostasis is stable within a certain interval of the parameters; the level of any interactions is determined and measured by the harm caused at the extreme limits. However, the harm is a relative notion: the safety and the harmless categories are not identical. The "no action" treatment can be safe but harmful because the uncontrolled disease harms, which we can stop by action. The acceptable changes in medical actions attempt to reestablish the normal, healthy homeostasis; or if it is not possible anymore, then it attempts to approach it as close as possible. The Hippocrates-phrase, "Nil nocere" also has to be understood in this way. Otherwise, the meaning is "Do nothing".

The internal transports, like the blood-stream, have a central role in keeping homeostasis. The blood circulation regulates multiple vital processes, including the heat exchange, to ensure the body's proper functional conditions. The blood-stream tries to compensate for the overheating by intensive perfusion and regulation of the vessels' flow-capacity. However, the regulation process of the blood-stream is non-linear. The quantitative analysis [33] shows the non-linear changes of the blood-flow in characteristic tissues varying by the temperature. The deviation (selection) of the tumor blood-flow starts just above 38˚C, **Figure 21**.

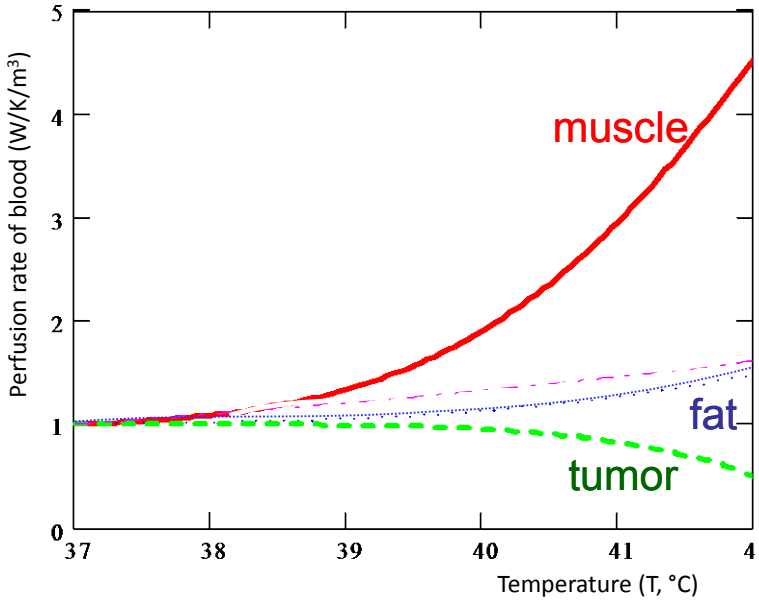

Figure 21. Relative quantitative changes of the blood-flow by a temperature increase in muscle, adipose tissue, and tumor lesion.

Due to the variation of the blood-flow, the necessary energy in a mass unit (specific absorption rate; SAR [W/kg]) non-linearly changes in the range between 39˚C - 42.5˚C [34] by the actual temperature, **Figure 22**.

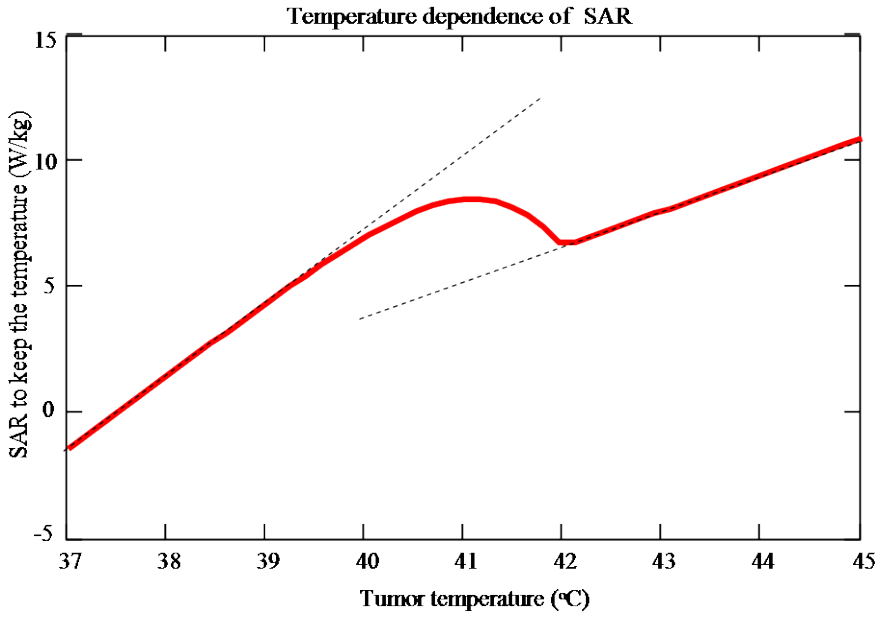

Figure 22. Variation of the requested specific absorption rate (SAR) to keep the given temperature in the tissue.

The non-linear regulation is general, using physiologic control by negative feedbacks. The promoter-suppressor action realizes the contraction of the feedbacks, which has a broad response-time for intervention.

3.3.1. The Selection Mode

The classical heating concept applies mass-heating of the entire tumor. The mass heating tries to be homogeneous in temperature (isotherm) and uses the temperature as the only control parameter. As previously discussed the temperature is usually measured in the nearby lumina or cavity and the same temperature must therefore be achieved in the lumina/cavity. The mEHT method uses a different paradigm, its heats the cancer-cells selectively in the tumor (**Figure 23**), using the malignant cells' unique thermal and electromagnetic characteristics.

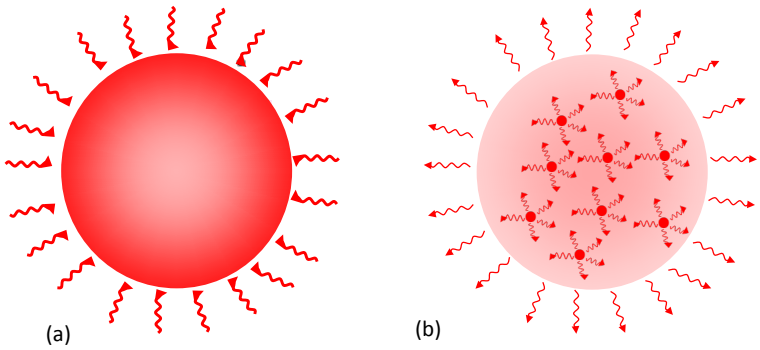

Figure 23. The differences between the heating paradigms: (a) Plane wave matching homogeneous heating causes energy-absorption in the complete target, while (b) impedance matching could be selective, heats only selected parts in a heterogenic manner, heating up the surrounded tissue by heat conduction (mEHT principle).

The selection uses the natural heterogeneity. The RF-current recognizes the electrical heterogeneity, and its heat effect results in thermal heterogeneity, resulting in the complex synergy of electric, and thermal processes [35], induces molecular changes driven by mEHT. The malignant differences make it possible to distinguish malignant cells from healthy cell structures [36]. The amount and composition of the extracellular aqueous electrolyte in the micro-environment of tumor cells massively differs from healthy tissues.

The malignant cells need a significantly higher energy amount than the healthy cells due to the intensive metabolism required to supply their proliferation [37]. The metabolic rate in most of the tumors is higher than their healthy counterpart (at least 15%, [38]), which selectively increases their temperature. The process has positive feedback because the higher temperature decreases the tissue's impedance [39]. Their metabolism requests a robust amount of nutrients which in the simplest way demands glucose. Due to the high level of necessary ATP production, the tumor cells predominantly perform simple anaerobic glycolysis instead of mitochondrial phosphorylation. The positron emission tomography (PET [40] [41]) identifies the extreme glucose intake in cancer cells. The rapid, intense fermentative process produces lactate, increasing the electrolyte's ionic conductivity in the cellular microenvironment, jointly with the higher in- and outflux transport of other ionic species. The increased ionic concentration means higher conductivity [42] of the microenvironment of tumor-cells, so it lowers the whole tumor's resistivity. This can be used to distinguish between

healthy and malignant situations [43]. The RF-current selectively flows through the low resistance (highly conductive) tumor rather than the more resistive healthy environment.

Malignant cells are autonomic, independently fighting for the energy against all other cells irrespective of healthy or fellow cancer-cells. For autonomy, they break their networking bonds and stop direct intercellular communications. The bonds formed by adherent proteins and junctions mostly vanish. Due to the missing cellular network, the extracellular matrix of malignant cells has high dielectric permittivity, which can be used for selection [43]. The structure of the microenvironment rearranges due to the missing bonds [44]. The altered structure allows the recognition of the malignant cells by their dielectric properties, which modifies the applied RF current [45] [46]. A well-developed diagnostic method uses this phenomenon [47], and it is applied in mammography [48].

The permittivity and the conduction modify the complete impedance in the microenvironment of the malignant cells [5], allowing their selection in an automatic way, while the RF-current flows in the direction of low electric impedance. The RF-current-density (specially chosen frequency and modulation) self-selectively flows toward the malignant cells, which is measurable by MRI current density imaging, [49] [50] [51]. This effect is completely automatic, it follows all movements of the cells in real-time, actually solving the challenge of focusing. The direct MRI electrical impedance tomography confirms the feasibility of using the impedance differences for selection [52].

The broken bonds between the cells leave the transmembrane proteins unconnected. These transmembrane proteins group by lipid-protein interaction in the membrane. The concentration of lipid rafts on malignant cells' membranes is significantly higher than on the membrane of non-malignant cells. The impedance-selected malignant cells' dense lipid rafts become an easy target of energy absorption. The rafts' clusters absorb the energy from the RF-current selectively [53] because the rafts have significantly lower electric impedance than the surrounding isolating lipid membrane. The selective energy-absorption promoted by a characteristic frequency dispersion in the applied 13.56 MHz frequency range (β/δ dispersion [54]), and the Schwan effect [55]), targets the lipid-protein interactions and selects water-bound states [56] at the membrane, effectively focusing the energy on the target [57]. This way, the natural electric heterogeneities drive the selection for energy absorption automatically, constructing an "autofocusing" process.

Further selection could be realized by the structural differences of the malignant tissue from their healthy counterpart. Usually, the pathological investigation of biopsies utilizes these differences by image pattern recognition in the samples. The pathological pattern naturally affects the RF-current in-situ, allowing additional selection of cancer tissue in the body. The alterations of the pattern modify the cells' spatiotemporal interactions, which dynamically act via intercellular interactions. The well-chosen noise could transduce free energy for the cellular reactions [58]. The dynamic relations produce a noise of homeostatic

equilibrium, which is measured as a peculiar signal [59] [60]. This noise differs in malignancy versus healthy tissue and is measurable by the RF current [61]. The noise difference is the basis for the applied modulation on the RF carrier in the mEHT method [62]. The modulation is an information delivery to the malignant lesion. The applied time-fractal has such autocorrelation time-lags that well fit the apoptotic excitation processes and may also act in enzymatic catalysis [58]. The spectrum of the reaction-times and rates appears in the modulation frequencies. The mEHT method applies such modulation, which is in harmony with the homeostatic collective network.

The collective excitations comprise the non-local waves and activate the energy-flow in the homeostatic networks. These excitations are mostly in a low-frequency range, and the expected frequency spectrum follows the natural 1/f fluctuations. Simply speaking, the modulation acts in harmony with the natural collective processes, promoting them, like keeping the swing in motion using harmonic push. Both the multicellular networked and the unicellular autonomic states of cells maintain a balance which is probably realized by an electromagnetic route [63]. The FDA-approved TTF also uses this kind of interaction to arrest malignant cell-division [64]. The method of mEHT uses an electrical field to modify the polymerization processes in the mitotic phase of the cellular division [65] with fractal noise modulation for a complex effect.

Furthermore, the applied noise is an active harmonizing factor [66], which has an emerging physiological application [67]. The fluctuations of electrical properties have unique information related to cell-membrane processes [68]. The monitoring of the noise as fluctuations in the complex system could be a factor in its surveillance [69]. Forcing harmony reconstructs the broken E-cadherin-beta-catenin cellular connections [70], which as was effectively and repeatedly demonstrated in an independent study [71]. The malignant cells' membrane is more rigid [72], while the cells themselves are softer than their neighboring healthy cells. The adherent connections and junctions could be formed only when the reactive ligands are close to each other.

As a result, the cellular connections have a geometric requirement to be re-established. The fermentative way of metabolism of malignant cells develops a strongly negative glycocalyx shell, which works against the proper geometric order, blocking bonding between the appropriate ligands. However, the extremely high fluctuating cataphoretic forces from the pink-noise modulation compensate the repulsion, and make the adherent connections possible.

The modulated carrier signal targets the selected malignant cells, and the cells rectify (demodulate) the received signal. The demodulation process uses two factors:

normal rectification by the highly polarized cell-membrane, [73] [74] [75].

stochastic resonance that makes the rectification, [76]

The non-temperature dependent rectification (non-linearity) was a question-mark for a long time because only linear attenuation was measured through the living object. The double membrane effect causes this apparent linearity. The

challenge is to measure the rectification in a tissue in which every cell with its opposite positions of the entry and exit points on the cell membrane acts like two diodes connected oppositely. So no rectification could be detected by measuring the tissue alone, Figure 24.

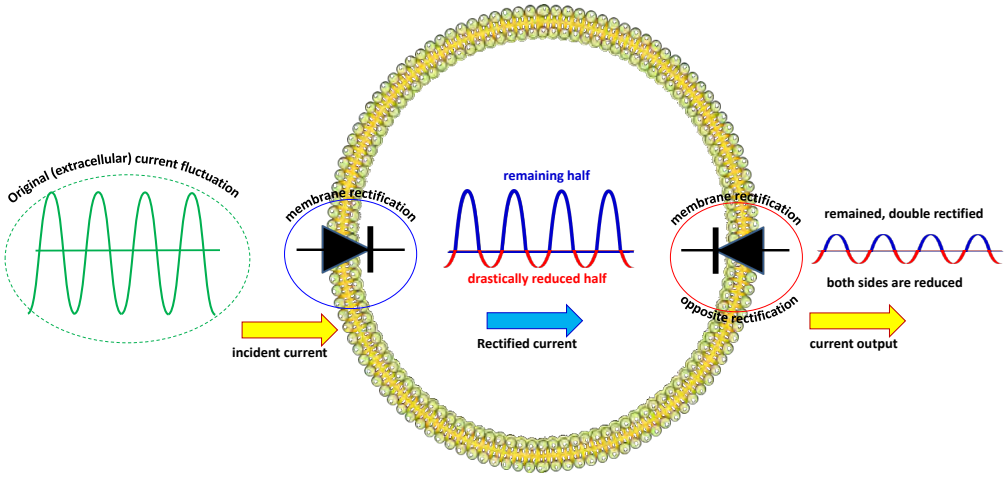

Figure 24. The symmetric but opposite rectification of the cell-membrane when the current goes through the cell makes the measured material linear, the rectification is not visible.

The mEHT impedance-matched capacitive coupling has four interconnected mechanisms for selection: the heterogeneities in conductivity and dielectric permittivity select the tumor, and its independent, while the membrane rafts absorb the energy in selected cells (the hyperthermia step), and the spatiotemporally distinguishable tumor-pattern provides an additional factor for selectivity, and isolation of the malignant cells, Figure 25.

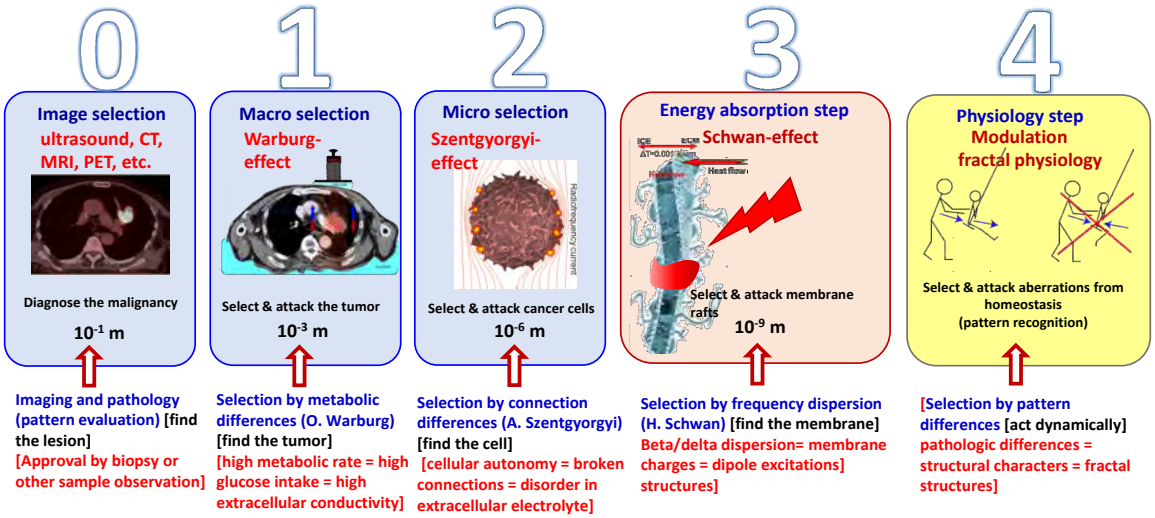

Figure 25. The steps of the mEHT action. (0) The conventional imaging supports the diagnosis; (1) The macro selection by conductive heterogeneities; (2) The micro-selection by the permittivity heterogeneities; (3) The energy absorption (the hyperthermia step) on the nano-range membrane raft; (4) A broad time-fractal spectrum recognizes and corrects the spatiotemporal pattern irregularities in the body.

Contrary to the above complex focusing (selection) mechanisms of mEHT, the plane-wave capacitive coupling methods regulate their approximate focussing of the energy by the size of the electrodes. The appropriately chosen electrode size is their focusing mechanism and their homogeneous mass-heating does not select on the cellular level.

The homogeneous heating has to balance the higher temperature and the increased blood-flow, induced by the intensive heating. The bloodstreams are a promising sensitizer of chemo- and radiotherapies, but are also a potential promoter of metastases resulting from the massive transport possibility of the cancer-cells. This process risks increase the metastases by forming circulating tumor cells (CTC). The CTCs could produce micrometastases throughout the entire body, which are not observable by the present imaging techniques. Heterogenic heating with microscopic (cellular) selection does not have such a challenge: the targeted particles can be supposed to have equal absorbed energy-doses, so the absorbed energy is the measured parameter. While the homogeneous heating method heats all parts of the target from outside, the heterogenic heating heats only the selected particles, and those heat the tumor where they are located. The selected particles are heated up intensively to have a higher temperature than their environment. The RF current at the <15 MHz frequency predominantly flows in the extracellular electrolyte. Its energy-absorption creates an active temperature gradient through the membrane [77], converting the electric heterogeneity to a thermal one. The mEHT heating does not make a massive general temperature increase of the targeted volume, macroscopically it presents a moderate temperature increase, but microscopically mEHT could produce extreme hyperthermia [78] [79]. The gradient causes the complete target's heating to the level of mild hyperthermia [80], which complements the applied chemo- and radiotherapies [81], but reduces the risk of metastases by CTCs. Notably, the pharmacokinetics of drugs are promoted by mEHT selective heating [82] [83].

The mEHT limits the increase of the SAR, which forces the development of the temperature. At a high temperature, the microscopic selection disappears, and an average temperature characterizes the target, like in plane-wave energy absorption **Figure 26**. For mEHT, the limited energy-absorption is mandatory.

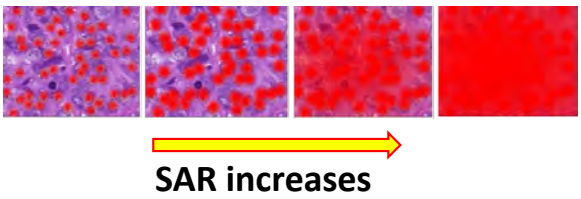

Figure 26. When the energy is too high, then everything is heated up, no selection could be seen. The selection factors became negligible. The selectivity has been lost, like the difference between the medicament and poison.

The electromagnetic selection mechanisms are general, and valid to all electromagnetic absorption methods treating cancer. However, the careful design

with focus on the precise selection emphasizes the anyway small effect. The emphasis of the selection over the thermal averaging needs the above factors, which consistently exceed the selection effects over the massive trend to homogeneous temperature averaging. On average, the relatively small SAR is high in the rafts, similar to the nanoparticle selective heating. However, the nanoparticles in mEHT are molecular clusters, which are sensitive to overheating. When the absorbed energy destroys the rafts by overheating them then the mEHT loses its largest advantage: the excitation of signal-transports for apoptosis and immunogenic cell-death.

A natural question arises: without the modulation is the effect of mEHT the same as other capacitive plane wave techniques applied at a lower power? The answer is yes, if their technical solutions fit the low energy, then they could form such complex situations as the modulation and the low-energy selection does.

However, it is not enough to have low energy alone; it must be that the energy is there where we need it, inside. For this, absolute fine-tuning (resonance to kill all imaginary part of the impedance), in order to promote the high current instead of the high voltage at the coupling, and the well-controlled radiation losses. An example for this fine tuning is how: the same Otto engine works in the high and low category cars. However, the same petrol makes different values for dynamism, the fuel consumption of the cars or the same electromotor principle gives different "output" efficiency in the electric car.

In summary, the specialization operates with precise electromagnetic impedance selection [84], using the heat on membrane rafts [53], and makes harmony by applying thermal [85], and non-thermal effects [86] [87]. The applied modulation well supports the precise selection of the malignant cells [85]. The mEHT breaks the paradigm that the physical conditions do not allow the proper biological effects, as researchers show from Charite University [88]. The electric concept in sequential magnification summarizes the main principle, **Figure 27**.

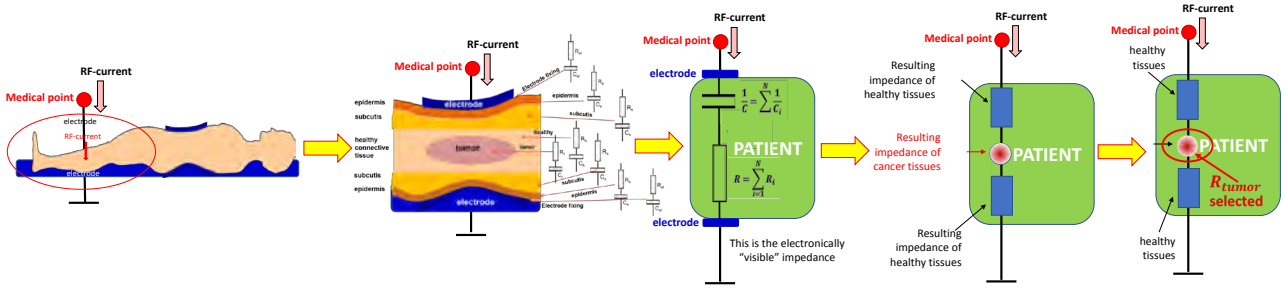

Figure 27. The series of the action of mEHT shows how it matches the focus on the tumor.

3.3.2. Penetration Depth

The penetration depth in the case of wave-absorption is the radiative penetration depth defined by the planar-wave absorption [89] [90], which is a loss of the absorbed specific energy or field in the body. The definition of the penetration depth of energy-absorption is the distance in the body when the initial 100% of

energy from the surface decreases by 1/e (remains only 37% of the energy). This does not mean blocking the beam deeper. It is an exponential function. We have practical knowledge about the X-ray diagnosis, which sees the deep lesions in the body. However, these X-rays have less penetration depth than 10 cm, Figure 28 [91].

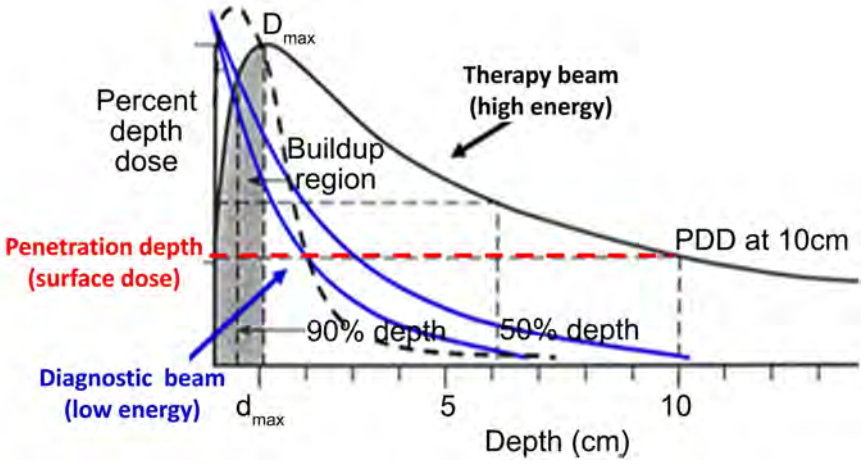

Figure 28. Diagnostic and therapeutical photon beams in X-ray radio diagnosis and therapy. Typical dose curves by photon (X-ray, γ-ray) radiation with typical penetration into dense tissues.

The beam continues its way in the body with 37% intensity, reaching the doubling of the penetration depth with 13.7% intensity, and so on, Figure 29.

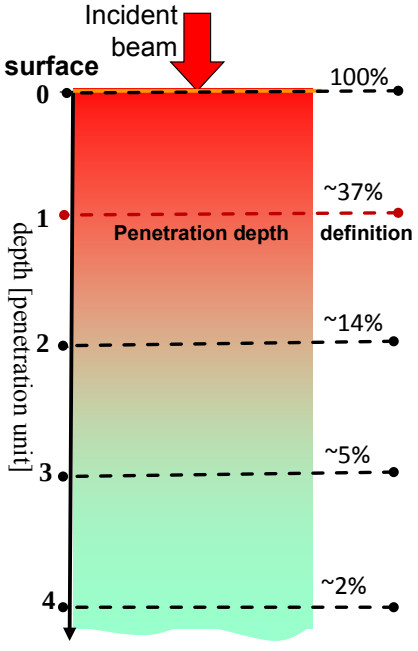

Figure 29. The principle of the definition of penetration depth: when the energy loss is 63% (remains 37%). Four times of penetration-depth, about 2% of the energy of the incident beam remains. This is the basis of X-ray diagnostic detection.

Assuming a patient with 20 cm thickness, the X-ray detection has less than 2% of the initial 100% beam intensity, but this is enough to construct an image, Figure 30 [92].

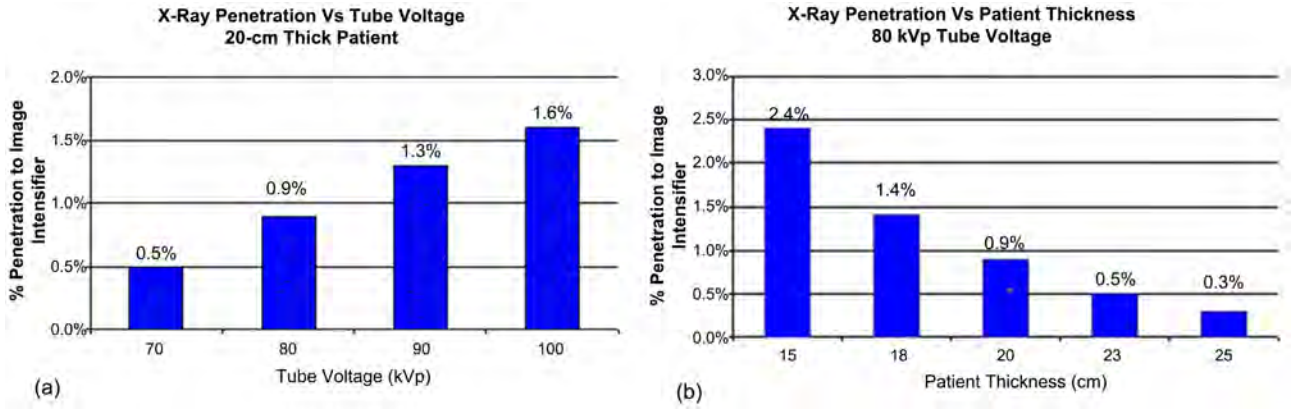

Figure 30. Typical intensities (percentage of the incident 100% beam) can be detected for X-ray images through the patient. In this case, and this tube voltage, the 20 cm patient thickness is approx. four times larger than the penetration depth. (a) Dependence of the voltage of the tube; (b) Dependence of the thickness of the patient at 80 kVp tube voltage.

In the case of electron-beam, the exponential loss is sharper, decreasing quickly, Figure 31 [93].

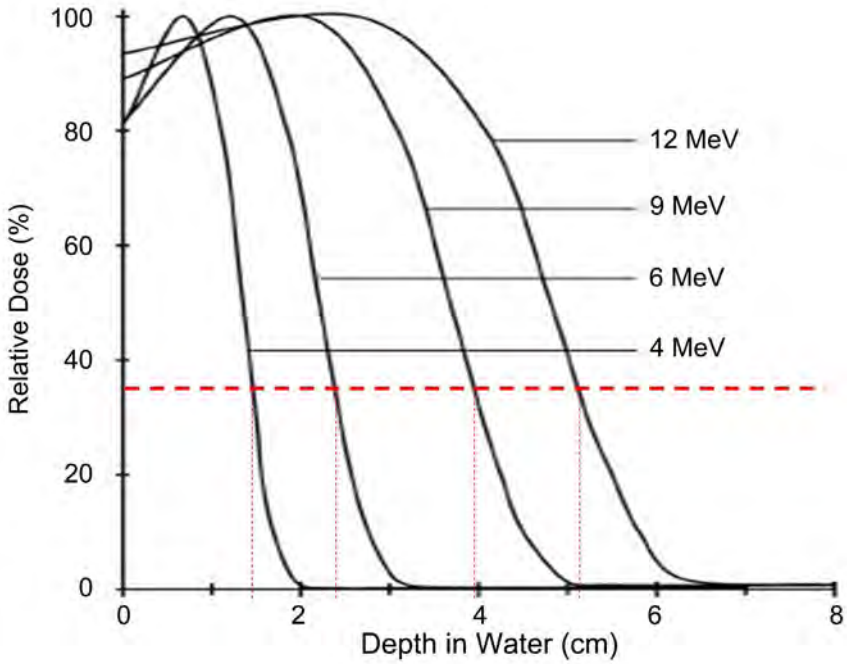

Figure 31. Penetration of electron-beam has a sharper decrease by depth. The definitive penetration depth is a few cm, shown with a dashed line.

In the case of non-ionizing radiation, the penetration is longer depending on the applied frequency (Figure 32) [94] and conductivity of the tissue (Figure 33) [94].

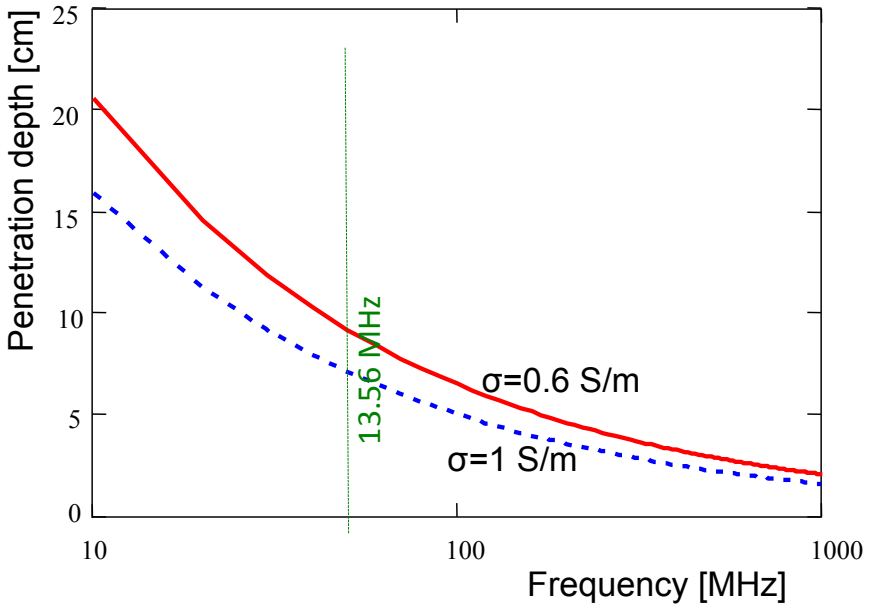

Figure 32. The penetration depth (37%) depends on the conductivity of the tissue. The average conductivity of muscle is approximately 0.5 S/m, so the penetration depth at 13.56 MHz frequency is about 17 cm. (at 8 MHz, it is approx. 20 cm.)

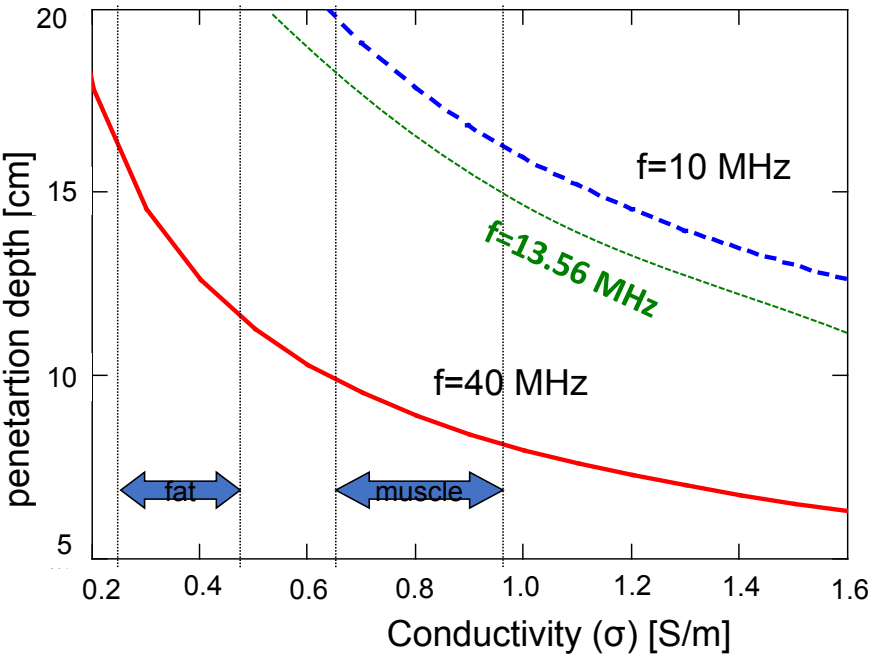

Figure 33. While the penetration depth is high in the fat, that absorbs a high energy value, leading to adipose burn. The apparent contradiction is the constrained increased voltage of the electrode required to push through the fatty tissue.

The jump of the electric field vector on the surface layer causes energy-absorption.

Measurements of the frequency dependence of the penetration depth in ex-vivo tissues show the correctness of the above considerations, Figure 34 [95].

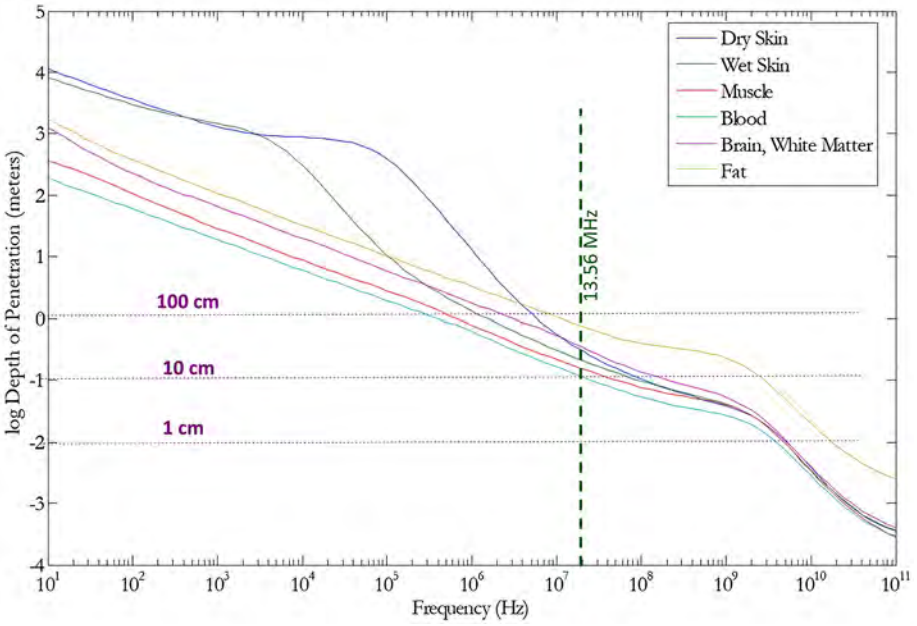

Figure 34. The penetration depth in various tissues vs. applied frequency. The 13.56 MHz is over 10 cm in all of the cases (the lowest is for blood, which is very good for selection). The penetration is rapidly decreasing by increasing frequency.

It is clear that the same forwarded energy exposition with identical energy-flow [W/m^2] can cause different energy-absorptions depending on the given conditions [96] [97], the actual organ [98], and the actual frequency [99]. The penetration depends on the electromagnetic parameters but does not depend on the patients' thickness. The impedance matching increases the penetration depth in homogeneous media by an additional 38%. (Note that the measurements and calculations assume homogeneous media.) The impedance matching selection focuses on the tumor-cells. The mEHT maximizes the RF-current, and only the focusing and the original energy deposit has importance [28]. The selection means that the real penetration is much more, and crosses the entire body.

3.3.3. Action Depth

Plane-wave capacitive coupling and all the homogeneous heating methods use only the heat to destroy the cancer-cells. The mEHT in its selective (heterogenic) heating combines the heat effect with the excitation of cellular signals. This fact modifies the induced processes' action depth as mEHT does not need such a massive energy-absorption as homogeneous heating needs in order to heat for the entire tumor-mass. We know very well that the real depth where the action is effective is an interval. For example, the effects of X-ray for apoptosis do not follow the decreasing energy-curve at the penetration. Even oppositely, it increases when the energy drops below a specific level, **Figure 35** [100]. This is because the smaller energy can generate bystander effects and so it can trigger apoptotic signals. This makes a complete interval for the apoptosis, which does not correlate with the penetration depth.

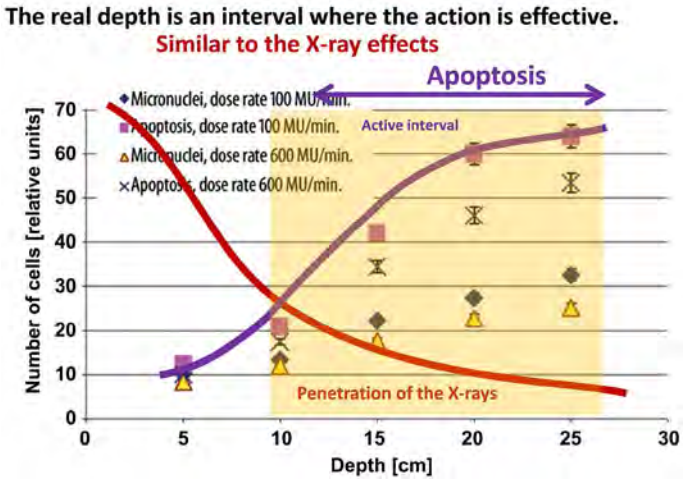

Figure 35. The number of cells with micronuclei, apoptosis as a medium depth function for 100 MU/min, and 600 MU/min dose rates, $p < 0.05$. Each point represents the mean value of three experiments; MU—Monitor Units (arbitrary).

The mEHT method also kills the malignant cells with apoptosis [101]. The apoptotic signal needs much less energy (and field) than the necrotic process [102], shown in the strict synergy of the heat and field effects [35]. The selection and initialization of the process are essential for this, which could happen by a few watts in-depth only. This is even more trivial when we see the immune effects, which are generated, act at distant sites [103], and have no real boundary with the observed abscopal effect [104]. In this meaning, instead of the penetration depth, we have to use the "depth of action," which defines the depth when the mEHT is active, even when the energy is less than the 37% of the incident beam, Figure 36.

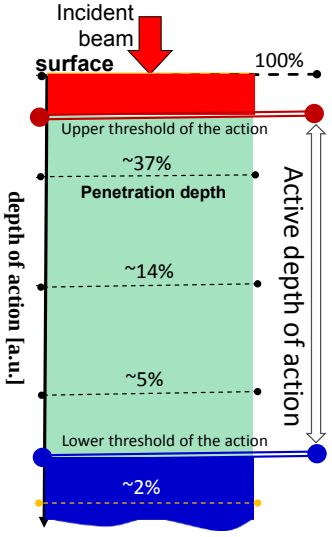

Figure 36. The active depth of mEHT is deeper than the average penetration depth because even 5 W could cause lethal apoptotic signals in selected cells. When the incident beam has 100 W energy, the depth when the mEHT is active could be three times the definitive (37 W) penetration depth.

The increased drug penetration and intensified pharmacokinetics by mEHT [82] [83] promote further elongation of the action depth.

In summary, the action depth for mEHT is deeper than the thickness of the patient's treated cross-sectional distance up to 60 cm (~200 cm circumflex of the cross-section).

3.3.4. The Dosing

Oncological hyperthermia presently faces multiple problems [19], where the most challenging is the lack of a clearly defined and measurable dose for clinical and research applications. The correct dose-definition of hyperthermia therapy is a critical issue in research and is crucial to the future of hyperthermia in oncology [105].

In a homogeneous heating approach, the dose considerations concentrate on the volume percentage, which could be considered having isothermal status. Complete homogeneity of heating of living objects could be achieved only in the WBH process, as LRHT has huge anatomical, physiological, bio-electromagnetic, and thermal heterogeneities, limiting the isodose-type approach. In the WBH process, the temperature was easily measurable and could be used for dosing the therapy. The proposed dose at present is the cumulative equivalent minutes referring to 43˚C: $CEM43\,T_x$ (measured in minutes) [106] [107] [108]; referring to necrotic cell killing at 43˚C. Due to the natural inhomogeneities, this dose contains the percentage of the target which has an approximately isothermal condition, denoted by T_x at the end of the practical applications [107]. For example, when the measured temperature is actually T_{90} in 90% of the monitored sites (referred to as the thermal isoeffect dose in 90% of the area).

In LRHT, the absorbed energy creates heat, but due to the non-linear feedback by transport properties (intensified blood and lymph flow), the situation is far from a state of equilibrium [109]. The blood-flow increases more in the healthy host tissues, causing a certain gradient of the flow intensity to heat the tumor's boundary. The most vivid, mostly proliferative layer of the tumor is near its border, so the cells which need the most heat-treatment remain at a lower temperature than the internal part of the tumor lesion, so the basic homogenous requirement is less realizable in the vivid tumor part than inside of its volume, which is often necrotic, without transport activity. The temperature dosing is problematic not only by the missing the isotherm condition but also because of its very complicated measurement.

Moreover, $CEM43\,T_x$ is controversial, it failed to show the local control characterization of clinical results in soft tissue sarcomas, [110], but was correlated with clinical results for superficial tumors [111]. When administering a dose of $CEM43\,T_{90}$ for local hyperthermia, it did not show a correlation between dose and clinical outcomes (like local remissions, local disease-free survival, and overall survival) [112]. It is calibrated by *in vitro* experiments [110], which are far from the reality of human medicine. Its necrotic reference at 43˚C makes this

dose unrealistic because in most human hyperthermia treatments, such a temperature is not reachable in the whole tumor. While the high temperature is realized in the ablation-like locality, the dosing by $CEM43\,T_x$ was false [113]. The inapplicability of this in-vitro calibrated dose is echoed in the whole-body hyperthermia (WBH) application, in which $CEM43\,T_{100}$ is very high (T_{100} means the complete isothermal heating of the tumor by the whole-body heating), but the results are very different from the same dose provided by local hyperthermia of the tumor lesion [114].

However, the challenge is that due to the considerable energy-loss in homogeneous heating processes, the temperature measurement is mandatory because otherwise there is no idea about the actual absorbed power in the target. In the method of mEHT, the measurement is not necessary in order to determine the absorbed power. The technique is able to accurately measure the absorbed energy by the incident beam [84]. Due to the high efficiency of current matching [115], the dosing of the treatment is simply calculable by the absorbed energy [64] [116] instead of by the complicated, inaccurate, and mostly invasive measurement of local temperature.

3.3.5. Heating Process

The homeostatic concept allows adaptation time for the physiological regulations to stabilize the actual homeostatic status. This complex approach requests a non-constant power during the treatment [117]. The simplest realization of the complex process involves step-up heating. The step-up heating is crucial. It has multiple additions to the success of mEHT:

- At electromagnetic heating, the stress is considerably focused on the cells which develop stress-proteins (HSPs) (chaperons to defend their status). The healthy cells rapidly develop 10-times more protective intracellular HSPs than the base level, while the stressful malignant cells only develop a maximum of 30% - 50% more of these intracellular proteins. This makes the healthy cells more protected compared to their malignant counterparts.
- The gradually increased HSP chaperones in malignant cells have time to go to the membrane and be liberated from the cell when the rafts are excited and the signals force their release (such selection does not occur in healthy cells). This liberation process is one of the factors of immunogenic cell death.
- The step-up heating supports the heating periods and upregulates the power when it starts to be saturated, which is optimal for the mEHT selection system.
- The step-up fits the homeostatic equilibrium, and so mEHT remains within the well-controllable quasi-linear physiological reactions.
- The sudden heating causes non-linear, non-controllable conditions, and the power shoots over the burning limit, and in most of the cases causes blisters (as is frequently reported by radiate heating methods). So the step-up method allows the control of homeostasis and helps the patient adapt to the ac-

tual energy-increase (I quote a famous experiment when a frog is in the water, which is slowly but gradually heated-up, the animal remains in hot water, even to its death, however, when you try to put a frog in hot water directly, it immediately tries to escape).

When the mEHT is applied strictly as a monotherapy, then step-down heating is necessary to block the neoangiogenic vessels. Due to the missing radio- or chemotherapy effect, the serious cases' metastatic spread has a higher probability, so blocking the vessels' immediately is crucial. But of course, the operating control in these cases has to be more strict.

Even in the step-up approach, the longer heating time tends to the homogenic temperature distribution due to the thermal equalization processes. To keep the non-homogeneous selection, periodic heating is also applicable, but it was only shown in preclinical applications [118].

3.4. Molecular Differences between the Effects of Impedance, and Plane-Wave Matching

The high energy absorption excites the rafts to trigger a signal transmission [78] [79]. The extrinsic signal transfer ignites apoptosis [101] [119] [120], **Figure 37**.

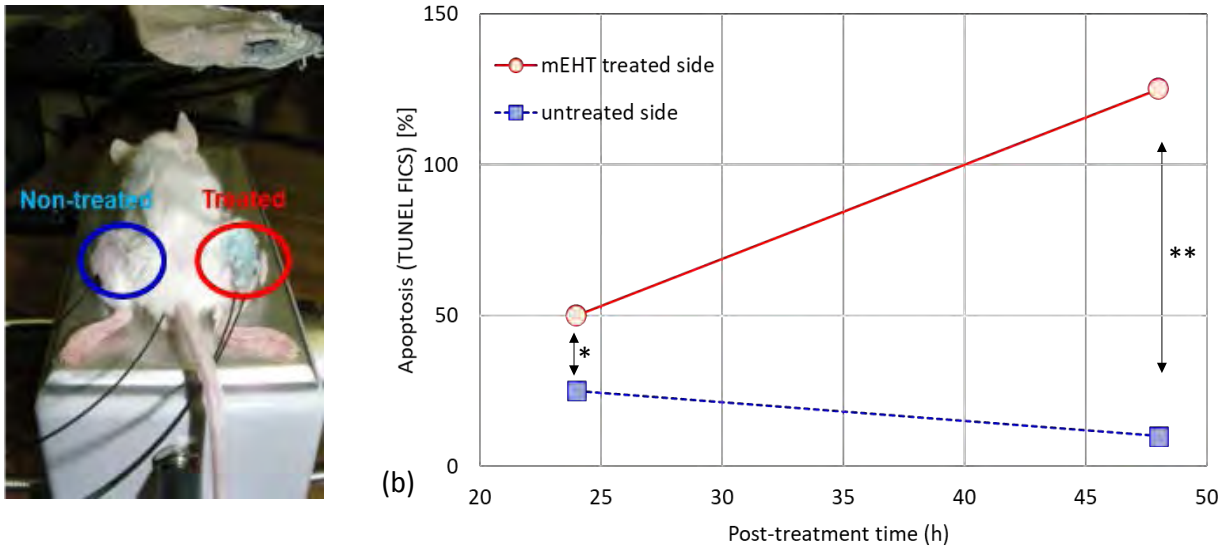

Figure 37. Late apoptosis measurement with TUNEL FICT method (Annexin V positive cells %) in HT29 cells (*in vivo*) 42˚C 30 min treatment parameters, two tumor animal models (a), results show a significant increase of apoptosis in the treated side.

The difference between the molecular effect of the two matching methods of capacitive coupling techniques has been effectively demonstrated *in vitro* [71]. The plane-wave capacitive hyperthermia (PWCHT) gives the same results as the naturally homogeneous water-bath hyperthermia (WBHT), as seen by the apoptotic processes including the reactive oxygen species (ROS) and calreticulin (**Figure 38**) [121].

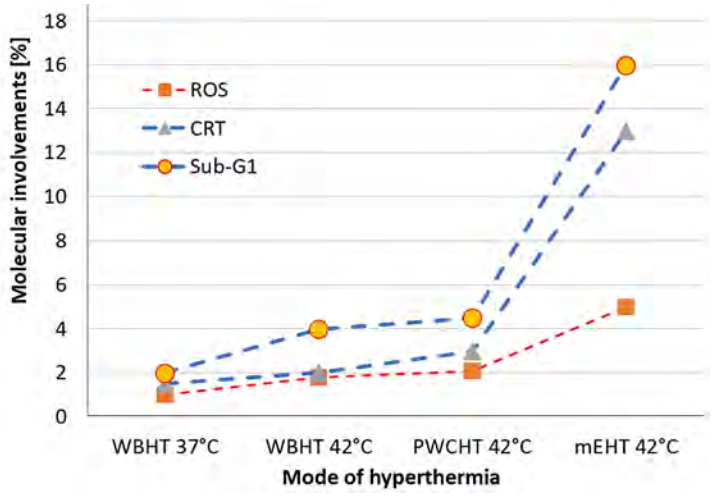

Figure 38. Molecular changes in Hepatoma (HepG2) cell-line *in vitro*. Apoptosis final state TUNEL (Annexin V positive cells %). WBHT—water bath hyperthermia (homogeneous heating reference at 37˚C and 42˚C); PWCHT—plane-wave capacitive hyperthermia at 42˚C, mEHT at 42˚C.

It is important to note that the purely homogeneous heating resulting from the water-bath hyperthermia (WBHT) produces comparable results to the plane-wave matching, indicating that plane-wave matching techniques also favour homogeneous heating, while mEHT differs significantly in the effects and outcomes. The apoptotic process involves a change in the potential of the mitochondria's membrane and the Ca^{2+} influx into the cell, **Figure 39** [122].

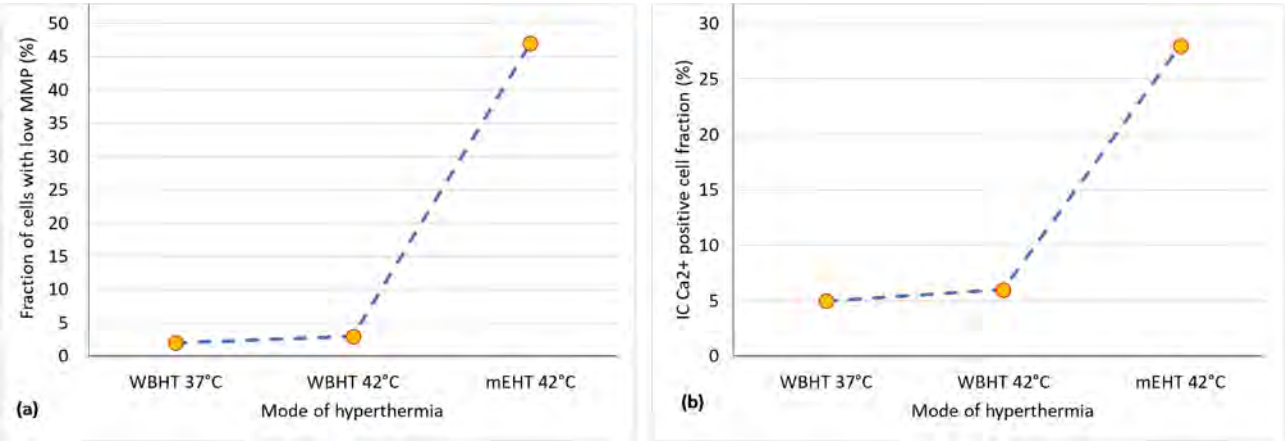

Figure 39. Comparison of heterogeneous heating caused by mEHT with homogeneous heating. (a) Fraction of cells with lowered mitochondrial membrane potential; (b) The calcium influx and intracellular ionic concentration (homogeneous (WBHT) heating reference at 37˚C and 42˚C, mEHT at 42˚C). Abb: WBHT—water bath hyperthermia, mEHT: modulated electro-hyperthermia.

The caspase developments' variants during the apoptosis require the extrinsic and intrinsic pathways (involving Caspases 8 and 9 **Figure 40**), and the caspase-independent signal routs [101]. Additionally, Septin4 blocks the XIAP, which makes free the extrinsic pathway from this suppressor [123]. All of these factors combined ensure apoptosis is the final result.

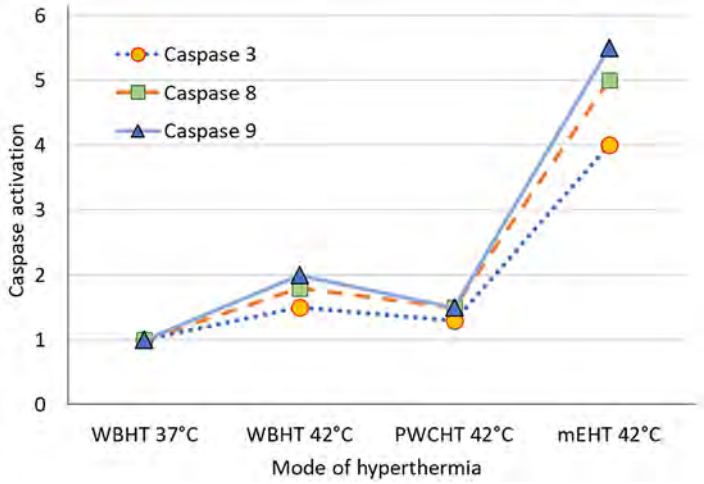

Figure 40. Caspase activation shows Caspase 8 and Caspase 9 for extrinsic and intrinsic pathways, respectively. WBHT—water bath hyperthermia (homogeneous heating reference at 37˚C and 42˚C); PWCHT—plane-wave capacitive hyperthermia at 42˚C, mEHT—modulated electro-hyperthermia at 42˚C.

The homogeneous heating results in energy-absorption in the tumor-mass, in an attempt to realize an isothermal situation. However, mEHT focuses the energy absorption on membrane rafts (nanoscopic size). The excess energy makes the extrinsic excitation of the apoptotic pathways (TRAIL-FAS-FADD complex), and makes the gradients through the cell-membrane, producing various thermal effects [79]. It increases the extracellular and the raft temperature to a level much higher than their environment. In consequence the calibration curves by measuring the apoptotic intensity significantly differ, **Figure 41** [35] [79]. It is clear that mEHT produces the same 25% relative cell-death as homogeneous heating in ≈3˚C lower temperature, which is an approximate difference between the local nano-temperature (at the membrane rafts) and the tumor-average temperature.

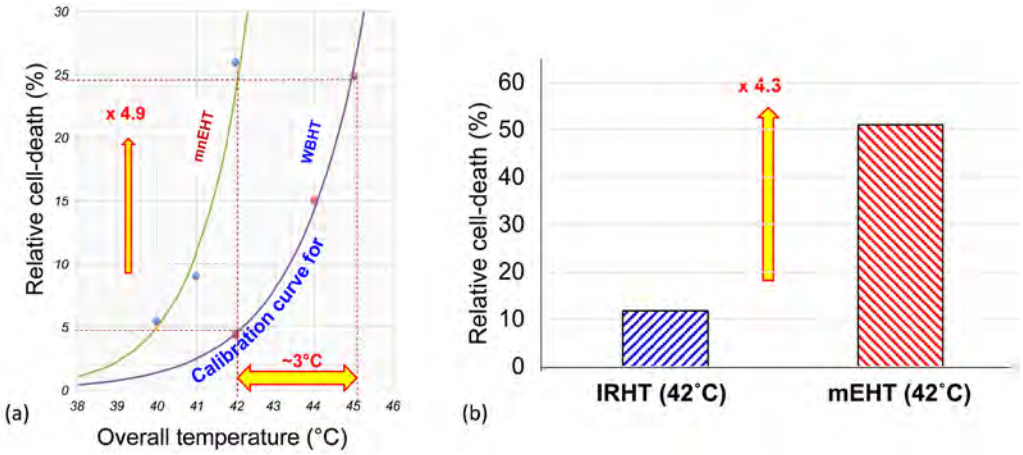

Figure 41. The relative cell-death (%) (a) *in vitro* [U937 cell-line] and (b) *in vivo* [HT-29 cell-line, xenograft]. The mEHT heterogeneous heating is >4 times more effective than the homogeneous technique at the 42˚C reference temperature. (IRHT—infrared, homogeneous heating technics).

In another experiment, a rough calibration comparison between mEHT and water-bath homogeneous heating shows even higher differences between the nano-scale and macro-average temperature, Figure 42.

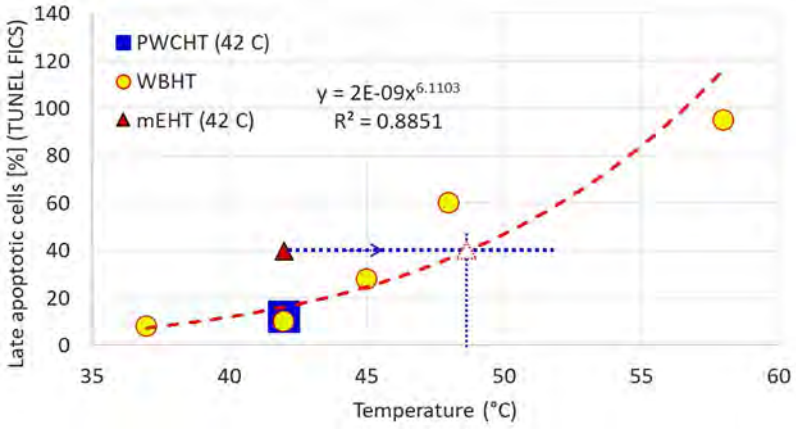

Figure 42. The temperature dependence of the apoptosis. The mEHT at 42˚C produces such apoptotic level, like homogeneopus heating does at >45˚C (WBHT—water bath hyperthermia (homogeneous heating reference); PWCHT—plane-wave capacitive hyperthermia at 42˚C, mEHT at 42˚C). (Apoptosis final state TUNEL (Annexin V positive cells %))

A direct temperature measurement of membrane rafts also shows a significant difference in a pilot experiment, Figure 43 [124].

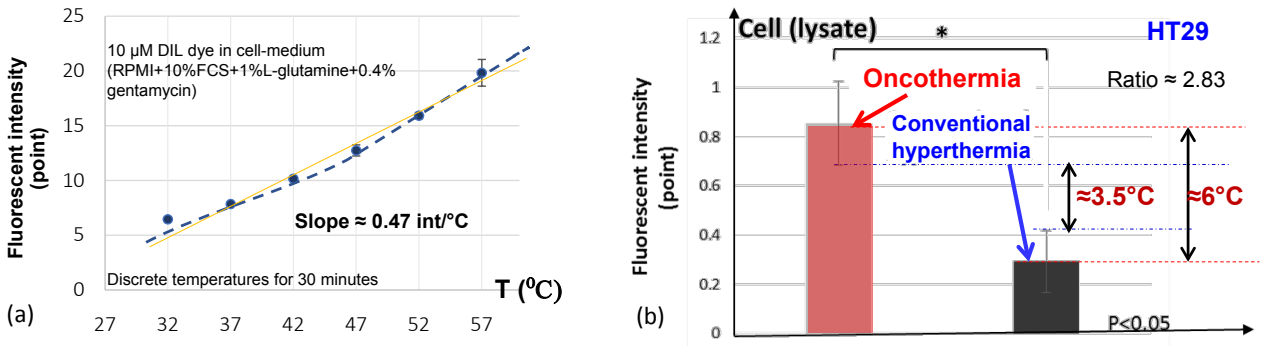

Figure 43. Membrane temperature measurement *in vivo* (mice, HT29 cells) 42˚C, 30 min. (a) *DIL* (Dilatometry)temperature calibration; (b) Fluorescent measurement, show the much higher temperature on the membrane of mEHT treated sample than on the membrane of the homogeneously (WBHT) heated one.

The heating certainly causes stress, producing chaperone proteins. The most characteristic protein family of chaperons is the heat shock protein 70 (HSP70). This protein has a double edge sword reaction: intracellularly it tries to avoid the cell's apoptosis, extracellularly it acts oppositely: it promotes the cellular apoptosis. Any kind of hyperthermia results in the expression of HSP70, but at different levels. Due to the large electromagnetic load that accompanies the heating processes, mEHT trigger the expression of more HSP70 than homogeneous heating, Figure 44. This difference is most significant 48 hours after treatment.

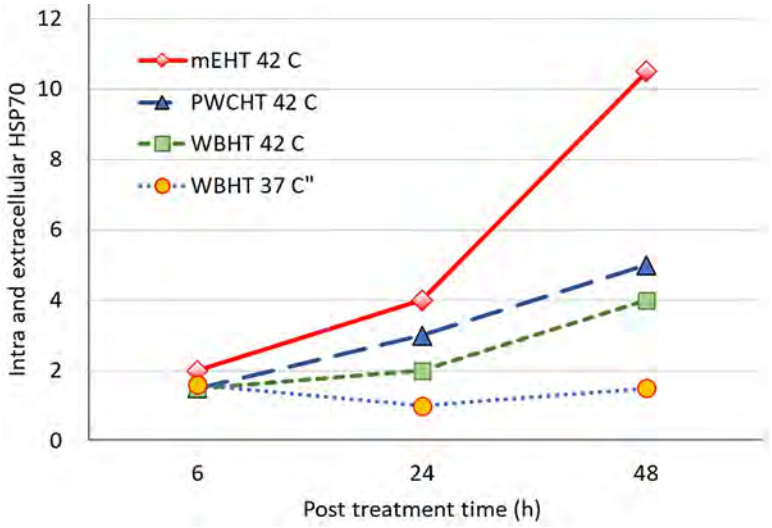

Figure 44. Comparison of the cleaved Caspase CD3+ expression. (WBHT—water bath hyperthermia (homogeneous heating reference); PWCHT—plane-wave capacitive hyperthermia at 42˚C, mEHT at 42˚C).

However, the location of the measured HSP70 is different. After 48 hours the concentration of the intracellular HSP70 returns to the level it was before the heating, but the extracellular levels increase, Figure 45 [125].

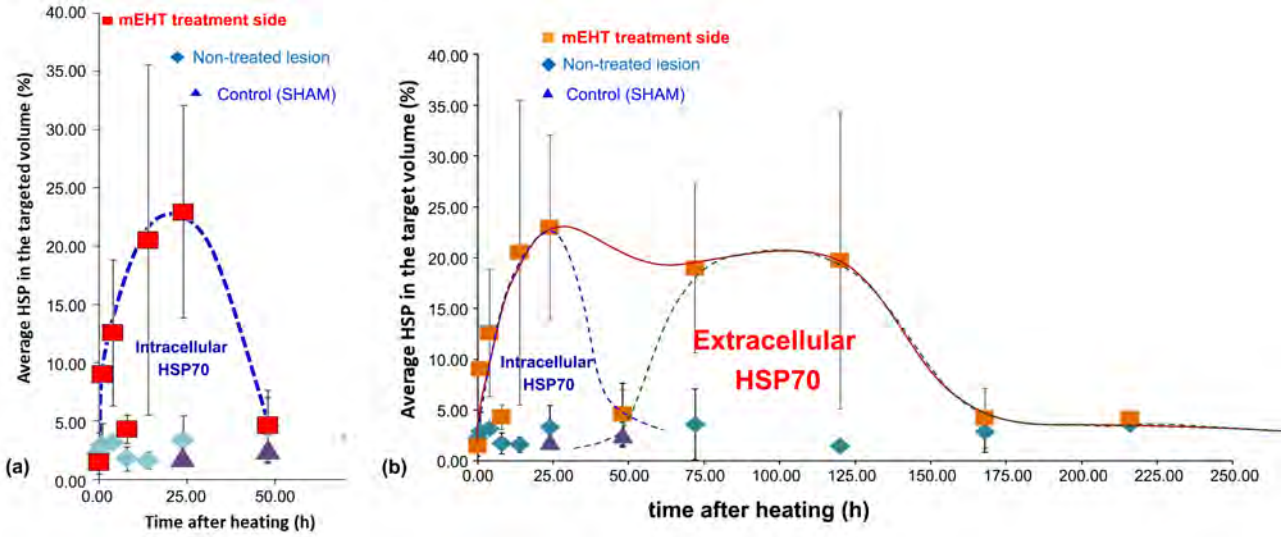

Figure 45. Development of HSP70 after mEHT treatment of *in vivo* xenograft mouse model (HT29 cell-line, at 42˚C, 30 min). (a) The level of HSP70 returned to the baseline level at 48 h post-treatment; (b) The development of the extracellular HSP70 only returns to the baseline level after a week.

A detailed review of cancer models describes the molecular mechanisms of mEHT [126].

3.4.1. Immunogenic Cell-Death

The apoptosic process caused by mEHT causes special immunogenic type of changes, allowing the genetic information to form antigen-presenting cell (APC)

by the maturation of the dendritic cells (DCs) or the macrophages. The excitation of the actual membrane rafts initiates immunogenic cell death (ICD). This process starts by producing a particular damage-associated molecular pattern (DAMP) (**Figure 46**) [127].

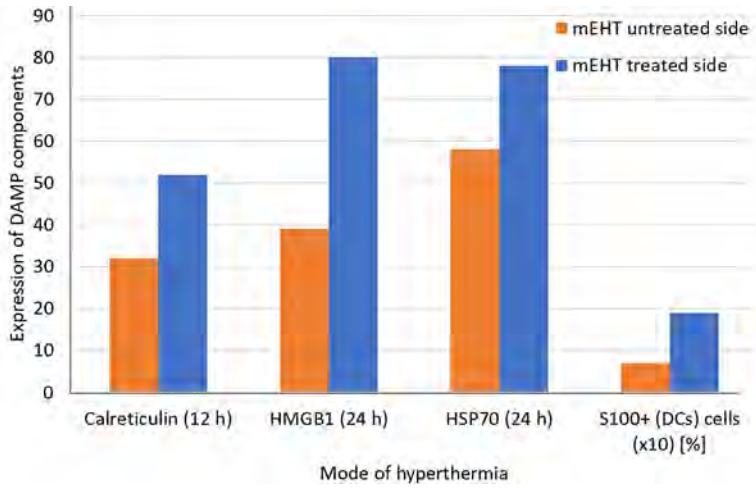

Figure 46. The DAMP development *in vivo* in an allograft mouse model (CT26 cells).

The proper signal transfer, and DAMP production could be limited or blocked by too much energy absorption on the rafts, which destroys it instead of exciting the transmembrane proteins, and receptors. The high energy-absorption may ignite phase transition mechanisms. For example, the kink in the Arrhenius plot at ~42.5˚C is probably a lipid-associated phase transition [128] [129] [130], which could lower the activation energy needed to facilitate the desired changes [131]. The change in the kink is expected to be influenced by the blood flow [33]. Among such conditions, the immunogenic cell-death is seldom, and also the APC and the immune actions will not be produced, because the temperature is high, and the membrane phase-transition makes hard producing apoptotic bodies. Well-defined sequences and spatio-temporal actions are necessary for the DAMP, which high energy technologies are not able to do. The possible small amount of proper DAMP production by high energy technologies would be disrupted, resulting in a mixture of effects, as is often observed many hyperthermia studies. This causes inconsistent results as there is no control of the processes in the complex dynamical network seen at a nanoscopic level.

3.4.2. Tumor-Specific Immune Effect

The main effect of mEHT is the energy absorption, like in all hyperthermia treatments, but it is further enhanced by the selection mechanisms, which makes it heterogenic, targeting, and energy-focused. The bio-electromagnetic and structural differences of malignancies appear in their spatial and temporal self-organized fractal structure, harnessed by the modulation effect. The DAMP-ICD associated tumor-specific immune effect is active in the entire body and therefore acts as vaccination. The re-challenge of the body with the same

malignancy therefore be expected to be unsuccessful [121]. It is an excellent advantage that without any invasive sampling and extra laboratory preparation, the immune effect is in situ and real-time.

Studies with DC, **Figure 47** [121]; and Marsdenia Tenacissima (MTE), **Figure 48** [127] as an immune-support suggest that when the patient's immune system is weak, due to tumor-development and the side effects of the previous treatments, additional immune support could help for complete action.

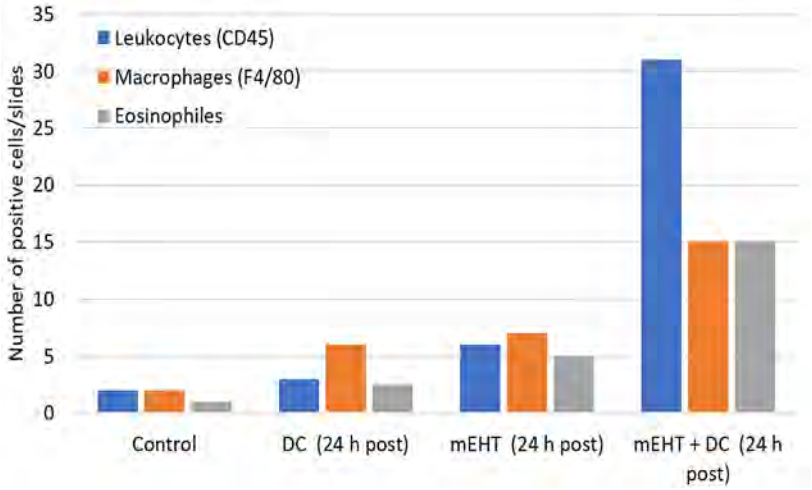

Figure 47. Immune invasion at the tumor 24 h post-treatment (DC—dendritic cell injection).

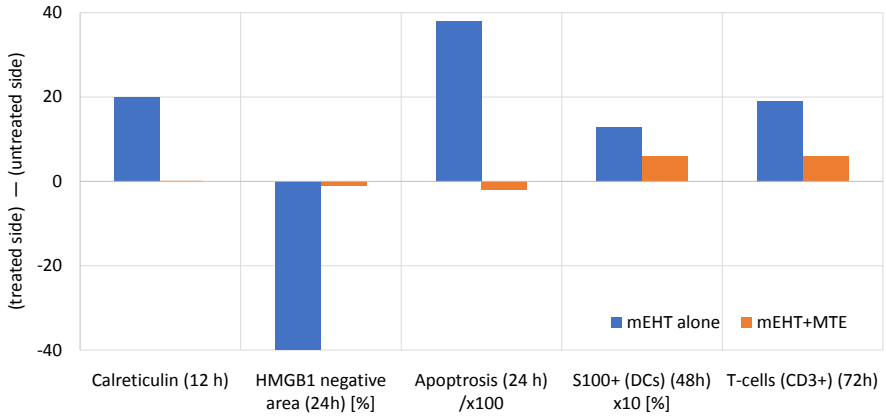

Figure 48. Effect of the immune-support Marsdenia Tenacissima (MTE).

This way, mEHT can create a favorable tumor microenvironment for an immunological chain reaction, improving the success rate of intratumoral dendritic cell immunotherapy [104] [121]. The applied paradigm's strategic point is that our task is to help the body recognize and destroy the malignancy. Targeting a product (such as weak points of tumor growth or simple destruction of the cell by thermal necrosis) could not repair the complex system. The entire process has to be targeted in order to re-establish the healthy state [132]. Developing a tumor-specific immune reaction directly drives the immune system to reparation.

The mEHT method recognizes the tumor by its biophysical, mainly electric impedance parameters, which at the same time has diagnostic value, Figure 49 [104] [133] [134].

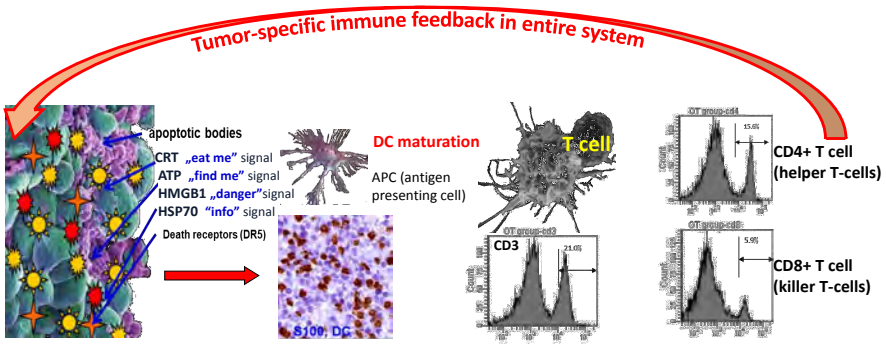

Figure 49. Producing the tumor-specific immune reaction. The gentle apoptosis produces DAMP and ICD presenting genetic information to antigen-presenting cells (APCs) which produces killer T-cells which are active in the entire body. (Works like a tumor-vaccination.)

The mEHT in this combination is a typical theranostic [135] therapy, which could be applied in combination with other standard tumor therapies like chemotherapies [136] [137], radiotherapies [138] [139], or check-point inhibitors [140]. A promising immunological approach is the combination of mEHT with viral therapies [141] [142].

3.5. Clinical Applications

A review of the clinical pieces of evidence of mEHT summarized essential clinical evidence [143]. The clinical trials are summarized in Table 1.

Table 1. Clinical trials that used mEHT in combination with other treatments.

No.	Tumor site	Number of patients	Treatment used	Results	Reference
1	Relapsed high-grade gliomas	15	mEHT + alkylating chemotherapy	Tolerable and safe for patients with relapses by high escalation of the dose too.	Wismeth, *et al.* 2010 [144]
2	Advanced gliomas	12	Chemotherapy, radiotherapy + mEHT	CR = 1, PR = 2, RR = 25%. Median duration of response = 10 m. Median survival = 9 m, 25% survival rate at 1 year.	Fiorentini, Giovanis, *et al.* 2006 [145]
3	Relapsed malignant gliomas	24	mEHT	Median survival = 19.5 months, 55% survival rate at 1 year, 15% at 2 years.	Fiorentini, Sarti, *et al.* 2018 [146]
4	Advanced glioblastoma	60	mEHT + immunotherapy	No added toxicity by immunotherapy. Median progression-free survival (PFS) = 13 m. Median follow up 17 m, median OS was not reached. Estimated OS at 30 m was 58%.	Van Gool, *et al.* 2018 [142]
5	Various brain-gliomas	140	Chemotherapy + radiotherapy + mEHT	OS = 20.4 m. mEHT was safe and well tolerated.	Sahinbas, *et al.* 2007 [147]
6	High-grade gliomas	179	mEHT + radiotherapy + chemotherapy	Longstanding complete and partial remissions after recurrence in both groups.	Hager, Groenemeyer, *et al.* 2008 [148]

Continued

7	Glioblastoma & Astrocytoma	149	mEHT + radiotherapy + chemotherapy (BSC, palliative range)	5y-OS = 83% (AST) in mEHT vs. 5y-OS = 25% by BSC. 5y-OS = 3.5% in mEHT vs. 5y-OS = 1.2% by BSC for GBM. Median OS = 14 m of mEHT for GBM and OS = 16.5 m for AST.	Fiorentini, Sarti, *et al.* 2019b [149]
8	Advanced hepatocell. carcinoma	21	Chemotherapy + mEHT	PR = 1, CR = 0, SD = 11. Combined therapy was effective, and no major complications were observed.	Gadaleta-Caldarola, *et al.* 2014 [150],
9	Refractory hepatocell. carcinoma	22	mEHT + thermo-active agents (TAA) or mEHT without TAA	CR = 1, PR = 0. Median OS = 20.5 weeks. 50% showed evidence of increasing QoL and minimal toxicity.	Ferrari, Ponti *et al.* 2007 [151]
10	Small-cell lung cancer (SCLC)	22	Chemotherapy + mEHT	mEHT enhanced destroying the cancer cells. Improved the OS of patients too.	Lee, Haam *et al.* 2013 [152]
11	Advanced cervical cancer	236	Random. Phase III (chemoradiation alone (CHR) and mEHT group (mEHT + CHR) [preliminary data]	Preliminary data for first 100 participants. A positive trend in survival and local disease control by mEHT. No significant differences in acute adverse events or quality of life between the groups.	Minnaar, Baeyens *et al.* 2016 [153]
12	Advanced cervical cancer	38	Chemotherapy + /− mEHT	The overall response (CR + PR + SD vs. PD) to was significantly greater with mEHT. No complications or extra adverse effect by mEHT.	Lee, Lee *et al.* 2017 [136]
13	Advanced cervical cancer	72	Radiotherapy + chemotherapy + mEHT	CR + PR = 73.5%; SD = 14.7%. The addition of mEHT increased the QoL and OS.	Pesti, *et al.* 2013 [139]
14	Advanced cervical carcinoma	20	mEHT + radiotherapy + chemotherapy	mEHT increases the peri-tumour temperature and blood flow in human cervical tumours, promoting the radiotherapy + chemotherapy.	Lee, Kim, *et al.* 2018 [154]
15	Advanced cervical carcinoma	108	mEHT + chemoradiotherapy	The metabolicly complete remnission (CMR) of disease outside the radiation field at 6 m post-treatment shows abscopal effect, significantly associated with the addition of mEHT.	Minnaar, Kotzen, *et al.* 2020b [155]
16	Advanced cervical carcinoma	206	Random. Phase III (chemoradiation alone (CHR) and mEHT group (mEHT + CHR) [preliminary data]	Compliance to mEHT treatment was high (97% completed ≥8 treatments) with no significant differences in CRT-related toxicity between treatment groups or between HIV-positive and -negative participants.	Minnaar, Kotzen, *et al.* 2020a [156]
17	Advanced cervical carinoma	202	mEHT + chemoradiotherapy	Six month local disease-free survival (LDFS) = 38.6% for mEHT and LDFS = 19.8% without mEHT ($p = 0.003$). Local disease control (LDC) = 45.5% with mEHT LDC = 24.1% without mEHT; ($p = 0.003$).	Minnaar, Kotzen, *et al.* 2019 [157]
18	Stage III-IV NSCLC	15	Ascorbic acid (AA) infusion + mEHT	AA safely synergies with mEHT and well tolerated, no major adverse effects	Ou, Zhu, *et al.* 2017 [158],
19	Advanced NSCLC	97	mEHT + radiotherapy + chemotherapy	Median OS = 9.4 m with mEHT OS = 5.6 m without mEHT; ($p < 0.0001$). Median PFS = 3 m for mEHT and PFS = 1.85 m without mEHT; $p < 0.0001$.	Ou, Zhu, *et al.* 2020 [159]
20	Advanced NSCLC	311 (61 + 197 + 53)	Radiotherapy + chemotherapy + mEHT	Two centres PFY ($n = 61$), HTT ($n = 197$) control ($n = 53$). 80% (PFY), 80% (HTT) had distant metastases, conventional therapies failed. Median OS = 16.4 m (PFY), 15.6 m (HTT), 14 m (control); 1st y survival 67.2% (PFY), 64% (HTT), 26.5% (control).	Dani, Varkonyi, *et al.* 2011 + Szasz, 2014b [160]

Continued

21	Advanced NSCLC	44	Chemotherapy + ketogenic diet + hyperbaric oxygen + mEHT	Mean OS = 42.9 m, PFS = 41 m. No problems were encountered due to fasting, hypoglycemia, ketogenic diet, mEHT or hyperbaric oxygen therapy.	Iyikesici, 2019 [161],
22	Peritoneal carcinomatosis with malignant ascites	260	mEHT + traditional Chinese medicine (TCM) compared to intraperitoneal chemoinfusion (ICI)	The Objective response rate (OPR) = 77.7% in study group (mEHT + TCM) vs. OPR = 63.8% in the ICI group. The QoL = 49.2% vs. 32.3% in the active and control group. Adverse effect rate (AER) = 2.3% vs. 12.3%.	Pang, Zhang, *et al.* 2017 [162]
23	Advanced rectal cancer	76	mEHT + radiotherapy + chemotherapy	Downstaging + tumor regression, ypT0, and ypN0 was better with mEHT than without. No statistical significance.	You *et al.* 2020 [163]
24	Liver metastasis from colorectal cancer	80	Chemotherapy + mEHT	Median OS = 24.5 m, and expected (historical) OS = 11 m.	Hager, *et al.* 1999 [164]
25	Various types of sarcoma	13	Radiotherapy + chemotherapy + mEHT	Primary, recurrent, and metastatic sarcomas responded to mEHT, the masses regressed.	Jeung, *et al.* 2015 [165]
26	Soft-tissue sarcoma	24	Chemotherapy + mEHT	Pathological response rate (pRR) = 42% in neoadjuvant chemo-hyperthermia treatment median OS = 31 m.	Volovat, Volovat *et al.* 2014a [166]
27	Advanced pancreas carcinoma	25	mEHT + chemotherapy + ketogenic diet + oxygen therapy	Mean follow-up = 25.4 m, median OS = 15.8 m, median PFS = 15.8 m.	Iyikesici, 2020a [167]
28	Advanced pancreas carcinoma	26	Chemotherapy + mEHT	SD = 9 (48%), PR = 4 (21%) PD = 6 (31%)	Volovat, Volovat *et al.* 2014b [168]
29	Advanced pancreas	106	mEHT + radiotherapy + chemotherapy	After 3 m, PR = 22 (64.7%), SD = 10 (29.4%), PD = 2 (8.3%) with mEHT after 3 m of the therapy. In group without mEHT in the same time: PR = 3 (8.3%), SD = 10 (27.8%), PD = 23 (34.3%). The median OS = 18 m with mEHT and OS = 10.9 m without mEHT.	Fiorentini, Sarti, *et al.* 2019[a] [169],
30	Advanced pancreas carcinoma	20	Enzyme-therapy + immunolo-modulation + hormone therapy + mEHT	Median OS > 10 m. Most patients experienced partially excellent improvement of QoL.	Hager, Süsse, *et al.* 1994 [170]
31	Advanced pancreas carcinoma	133 (26 + 73 + 34)	Radiotherapy + chemotherapy + mEHT	Two centres PFY ($n = 26$), HTT ($n = 73$) control ($n = 34$). 59% (PFY), 88% (HTT) had distant metastases, conventional therapies failed. Median OS = 12.0 m (PFY), 12.7 m (HTT), 6.5 m (control); 1st y survival 46.2% (PFY), 52.1% (HTT), 26.5% (control) QoL was improved.	Dani, Varkonyi, *et al.* 2008 [171]
32	Ovarian cancer	19	mEHT with dose escalation	The mEHT treatment was feasible in patients with recurrent or progressive ovarian cancer without any complication.	Yoo *et al.* 2019 [163],
33	Metastatic cancers (colorectal, ovarian, breast)	23	mEHT + radio-therapy + chemotherapy	OS and time to progression (TTP) were influenced by the number of chemotherapy cycles ($p < 0.001$) and mEHT sessions ($p < 0.001$). Bevacizumab-based chemotherapy with mEHT has a favorable tumor response, is feasible and well tolerated for metastatic cancer patients.	Ranieri, *et al.* 2017 [172]

Continued

34	Different types of metastatic/recurrent cancers	33	mEHT + radiotherapy	CR = 2 (6.1%), Very good PR = 5 (15.2%), PR = 13 (39.4%), SD = 9 (27.3%), PD = 4 (12.1%). Three patients (9.1%) developed autoimmune toxicities. All these three ptients had long-lasting abscopal responses outside the irradiated area.	Chi, Mehta, *et al.* 2020 [173]
35	Advanced gastric cancer	24	mEHT + chemotherapy + ketogenic diet + oxygen therapy	CR = 22 (88%) Mean follow-up = 23.9 m, mean OS = 39.5 m, mean PFS = 36.5 m,	Iyikesici, 2020b [174],
36	Various		mEHT + chemotherapy	The feasibility and success of oncothermia is proven.	Fiorentini 2020 [175]
37	GBM		mEHT + chemotherapy	The feasibility and success of oncothermia is proven.	Van Gool 2021 [176]
38	Rectal cancer	120	mEHT + radiotherapy + surgery	In mEHT group, 80.7% showed down-staging compared with 67.2% in non-mEHT group.	Kim 2021 [177],
39	Gliomas	164	mEHT + chemotherapy + radiotherapy	CR + PR is 41.4% for mEHT and 33.4% for conventional therapies.	Fiorentini 2020 [178]
40	Gastrointestinal cancer	34	mEHT + chemotherapy	The feasibility and success of oncothermia is proven.	Garay 2020 [179]
41	Ovarian, cervical cancer		mEHT + chemotherapy + radiotherapy	The feasibility and success of oncothermia is proven.	Wookyeom 2018 [180],
42	Breast cancer	13	mEHT + chemotherapy + surgery	The feasibility and success of oncothermia is proven.	Szasz AM 2020 [181]
43	Cervical cancer	38	mEHT + chemotherapy	Cox-regression for CTx + mEHT study-group, (Rs-variable time-ratio of start of mEHT compared to OS (overall survival) Coefficient = 6.1, CI (95%) = 7.96; StErr = 4.06, $p = 0.13$, Hazard = 449.	Lee 2020 [81]
44	Various sites	277	mEHT + chemotherapy	52% of the entire group was subjected to result analysis. 48% was not traceable. The result of the 52% was 21.5% PR, 36% SD, 28.9% PD, and 12.6% exitus. So 58.5% of the patients showed either stable disease or partial remission.	Lee 2013 [182]
45	Various sites	784	mEHT + chemotherapy + radiotherapy + surgery	Preliminary results show promising survival trajectories. mEHT is a safe treatment with very few adverse events or side effects, allowing patients to maintain a higher quality of life.	Parmar 2020 [183]
46	Various sites		mEHT + chemotherapy + radiotherapy	Planned trial	Arrojo 2020 [184]
47	Various sites		mEHT + chemotherapy + radiotherapy	The feasibility and success of oncothermia is proven.	Szasz AM 2019 [143]
48	Brain tumor	54	mEHT + chemotherapy	mEHT strongly and significantly enhances the efficacy of the ddTMZ 21/28 d regimen ($p = 0.011$), with a maximum attainable MST of 10.10 months (95%CI 9.10 to 11.10).	Roussakow 2017 [185]

4. Conclusions

The two variants of capacitive coupling, the plane-wave, and impedance matching, make different treatment applications in preclinical experiments and human

medical applications. Technically the difference between these capacitive methods is the design for homogeneous or heterogeneous heating. The homogeneous heating needs to measure the target's temperature, obtaining information about the amount of absorbed energy, while the impedance matching gets direct information about the energy-absorption. This results in a difference in the dosing method because, in the homogeneous approach, the temperature is the mandatory part of the heating dose, while in the heterogeneous case, the absorbed energy characterizes the process. The heterogeneous heating without artificial nanoparticles is realized in the mEHT method. This method has special qualities which improve the conventional hyperthermia results:

1) Excites apoptotic signals by extrinsic pathways.

2) Though the selected membrane rafts, mEHT excites the TRAIL DR5 death-receptor (with FADD and FAS complex), and this extrinsic excitation triggers the ICD.

3) The raft excitation triggers the DAMP and ICD, crucial for the immunogenic (abscopal) effect. This turns the local treatment into a systemic treatment, shown in the elongation of the survival time, without being limited to local control.

4) The immunogenic effect is vital for the cases with far advanced, relapsed, metastatic disease, and not only locally advanced cases.

Acknowledgements

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Conflicts of Interest

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

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Therapeutic Basis of Electromagnetic Resonances and Signal-Modulation

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Abstract

The medical application of electromagnetic resonances is a controversial area of knowledge. Numerous unproven statements and some medical quackeries were published and distributed in informal channels among suffering patients. The fake information is hazardous in such severe diseases as cancer. The optimal, high efficacy energy transport by resonances attracts the interest of the experts and the public. The focus of the attention is technical and concentrates on the careful selection and excitation of the target compounds or cells, expecting helpful modifications. The complication is the complexity of the living systems. The targets are interconnected with an extensive network in the tissues where homeostasis, a dynamic equilibrium, regulates and controls changes. The broad range of energy-transfer variants could cause resonant effects, but the necessary criteria for the selection and proper action have numerous limits. The modulated high-frequency carrier may solve a part of the problem. This mixed solution uses the carrier and modulation's particular properties to solve some of the obstacles of selection and excitation processes. One of the advantages of modulation is its adaptive ability to the living complexity. The modulated signal uses the homeostatic time-fractal pattern ($1/f$ noise). The task involves finding and providing the best available mode to support the healthy state of the body. The body's reaction to the therapy remains natural; the modulation boosts the body's ability for the homeostatic regulation to reestablish the healthy state.

Keywords

Electric Impedance, Coherency, Complexity, Molecular Excitations, Collectivity, Homeostasis, Entropy, $1/f$-Noise, Time-Fractal

1. Introduction

The bioelectromagnetic effects attracted the significant attention of various re-

searchers and laypersons in the last couple of centuries. The observation shows that the electric and magnetic fields influence the biological processes. However, the therapeutic applications of bioelectromagnetics cause heated debates from its start described it as "humbug" [1] and "utter idiocy" [2]. The weak proofs well support the medical skepticism nowadays too [3] [4]. Many patented ideas like Lakhovsky's radio-cellular-oscillator [5] [6], the Priore's electromagnetic therapy [7] [8] [9], deal with the bioelectromagnetic therapy, without any proof, creditable systematic studies, only some positive case-reports were published. Others, like Gurvich's mitotic wave in mitosis and some enzymatic reactions [10], have no tools, which are sensitive enough to measure the supposed effects [11]. Even such genius giant as Nikola Tesla had patented a method about the high-frequency oscillators for electro-therapeutics, using "ultraviolet rays", [12] presently also out of convincing data.

One of the most influential ideas in the bioresonance field was developed by Royal Raymond Rife. The "resonance topic" started with a revolutionary step of optical microscopy [13]. The Rife-microscope had the ultimate resolution in that time [14], able to record time-lapse movies of microbes [15]. Various pathogen organisms show cellular damages at "resonant frequencies". The phenomenon was described with "mortal oscillatory rate" (MOR) [16] [17] [18] [19]. The cancer-cells had showed also mortality by resonances [19] [20]. Strong critical opinions appeared about the method [21] [22], and the electronic devices for cancer management [23]. The lack of pieces of evidence, the selected favorable cases formed the "pseudomedicine" supported by electronics [24]. The fraudulent activities were punished [25] [26].

The role of bioelectromagnetics and especially the resonance phenomena became the "battlefield" of science with multiple quackeries and unscientific theories. The serious doubts make this topic an impossible research venture. Notwithstanding the importance of this great challenge, this work aims to study the possible application of electromagnetic resonances and modulation in cancer therapies.

2. Challenge of Complexity

The living systems are complex, well self-regulated, and controlled. The molecular biology's deterministic approach, about the completeness of the molecular development, strictly follows the stored model of the whole system in the DNA. However, the living processes are more complex than enough computer capacity could describe the system. Reducing life to a simple deterministic approach (reductionism) loses the system as an interconnected and complexly regulated unit. The proper consideration is to handle the living system as a whole (holism).

The biological systems have the same complementary duality as the particles in quantum mechanics have. Nested and overlapping levels of the observation depend on the scale of the studied part of the system [27], an inspection of the same living feature from different points of view. This phenomenon is similar to

the quantum duality, the observation depends on the observer also: "A living thing cannot be explained in terms of its parts but only in terms of the organization of these parts" [28].

It is more challenging that the living complexity involves a logical incompleteness [29], discovered by Gödel almost a century ago [30]. The incomplete, complex situation means that we may address valid questions which have no answer in a deterministic way. These questions have a loop with a self-reference: first, the hen or the egg? The answer goes to the evolutionary field; and necessarily leaves the deterministic thinking. Similarly, the answer to the question "what existed first: the promoter or the suppressor" has no direct answer. A loop also needs a developmental, non-deterministic consideration. The complex system is regulated and controlled by primarily negative feedback loops, having the Gödelian incompleteness. Theoretical biology faces these challenges, which builds a "tragicomic" situation [31].

2.1. Homeostasis of Life

Biological systems and their macro- and micro-parts are energetically open, operate on various in- and outputs, causing a specified event. The product's reaction could amplify/promote the further shift or inhibit/block it, suppressing the change. The promoter-suppressor pairs work in sensitive order, modified by the feedback loops, the processes maintain the dynamic equilibrium of the living system, forming homeostasis. The homeostasis is far from the static equilibrium, but in normal conditions, it has a self-adjusted stationery state, regulated by the negative feedback. The feedback control mechanism regulates the promoter-suppressor balance in a relatively narrow predetermined range around the set-point value. The dynamic homeostatic equilibrium keeps the system stable but constantly changing. The dynamic equilibrium approaches to count "degrees of truth" rather than the usual "true or false" decisions [32]. Numerous negative feedback loops control the homeostasis [33] [34] in the micro and macro-structures levels.

The system's open character needs positive feedback processes too, which are one-promoting/accelerating the started process. Positive feedback results in more of a product or accelerates the progress.

The homeostasis governs the equilibria in all living ranges of space and time.

It is tuned by the intertwining of processes, which at each step seeks to have a dynamic and interconnected balance of suppressor-promoter pairs of the regulatory process [35].

The dynamic behavior of the interacting complexity guarantees robust stability. The regulation and controlling process are essentially inherently dynamical, so the term "homeodynamics" describes it better than "homeostasis" [36].

2.2. Self-Organizing

The living system exchanges energy with its environment, and every part, like the cells, tissues, and organs, has open energy trade with other parts of the sys-

tem. The spatiotemporal arrangement of the living organisms and their parts are self-organized [37] [38]. The self-organized feedbacks secure the stability against a relatively wide range of perturbations. The structures' self-similar building simplifies their construction by deterministically or statistically repeating the same template and connecting them with the same structure [39], building a self-similar harmony.

The systematically built structures are fractals, which commonly appear in natural forms [40]. The fractal description of living objects' spatial irregularities allows for an objective comparison of complex morphogenetic differences [41], and provides a useful tool to follow the physiological changes in pathologic processes [42]. Fractal models explain the structural developments of life processes [43]. The collectivity of the organization also could be monitored by the fractal concept [44].

The structural fractals complete the dynamic properties of life. The dynamical structures develop a complex spatiotemporal approach of biology, the fractal physiology [45] [46] [47], dealing with random stationary stochastic self-organizing processes in physiologic phenomena. Fractal physiology offers practical applications recognizing the diseases [48]. The self-similarity allows modeling cancer tissues by fractals [49], described by a generalized model [50]. The fractal geometry helps to evaluate the various images in oncology [51], describes the pathological architecture of tumors and their growth mechanisms accompanying time-dependent processes [52], and prognostic value [53].

The self-similar self-organizing process is collective [54] and relates to the allometric scaling of living species [55] [56]. The collectivity subordinates the individual needs to the groups and optimizes the energy distribution for the best survival with the lowest energy consumption. This energy-share works like some kind of democracy [57].

2.3. Stochastic Processes

The well-organized complex dynamic equilibrium characterizes the regulative activities of the living systems from genomic to global adaptation of the organisms to the environmental challenges [41]. The time-dependent processes realize the observed signal with a probability of requesting a stochastic approach instead of conventional thinking based on deterministic changes [58]. The homeostasis is often ignored and used as a static framework for effects [59]. The stochastic approach is fundamental in biological dynamism [60]. Deterministic reductionism can mislead the research.

Diagnostic parameters (signals) characterize the living organism. The average in time represents the measurement of signals, which fluctuate around the average value in a controlled band. The fluctuation sets various actual microstates in the body, only for a short time regarded as a signal's noise. The homeostatic control of the body regulates the fluctuations. The homeostasis needs "order" in noise structure parameters like frequencies, intensities, phases. The minimal

number of diagnostic signals describing in a state is defined by the quasi-independent, weakly overlapping regulation intervals. The number of these quasi-independent diagnostic signals does not change during the system meets the conditions of the healthy dynamical equilibrium. However, together with the relative constant averages with a standard deviation in the fluctuation band, the distribution of the signal frequencies varies. The variation depends on the adaptation to internal and environmental conditions. The measured quantities appear an average $\langle D_i \rangle$ of microscopic diagnostic states D_i. If the change of D_i remains within a tolerance band l_{D_i} around $\langle D_i \rangle$, the homeostasis is considered faultless, the subject is declared healthy.

The fluctuation of the signals around the actual average $f_{D_i} = D_i - \langle D_i \rangle$ opens a new possibility to study the living processes. The change in the fluctuation of the signal occurs sooner than the variation of the average value. However, the changing of the regulative processes could drastically modify the signal's fluctuation without changing their average value. The alterations in the noise spectrum can predict reorganizations of the regulative feedback, which could point a healthy adaptive process to the environmental challenges but could indicate disease as well. The various curative processes could reestablish the signal averages. Although the new reestablished average is the same as was the previous, the fluctuations around the average could differ from the previous dynamism. The interacting connections and regulating signal loops could vary the fluctuations from earlier. This variation happens for example, when the immune system develops new functions by "learning" the fight against pathogens. The systemic control is modified, and the system reflects it in the regulative fluctuations. Nevertheless, it could happen that the therapy reestablishes the proper average of the diagnosis signal, but the patient remains ill. The noise spectrum examination may recognize such incompatibilities, when the problem does not appear immediately in the averages. The opportunity of noise analysis is an accurate novel approach to diagnose and follow the illness in its early stages.

The power spectrum $S(f)$ characterizes the stochastic signal with the f frequency. The other important functional character of the signal is the autocorrelation ($R_{XX}(t_1, t_2)$), which measures how the signal correlates with itself with a delayed copy of itself. The correlation is displayed as a function of time-lag ($\tau = t_2 - t_1$) in X position. The $R_{XX}(t_1, t_2)$ is the similarity of the signal-parts having time delay between them. The autocorrelation evaluation is a mathematical tool for finding repeating patterns, looking for periodicity in the signal. It is a useful tool also to find a missing periodic signal, which we regard as an important component when a set of repeated interactions form the investigated fluctuation.

The simplest complex noise is Gaussian (the amplitudes have normal distribution), and its power function $S(f)$ is self-similar through many orders of magnitudes. The $S(f)$ is characterized with α in a simple form, like in (1)

$$S(f) = \frac{A}{f^{\alpha}} \tag{1}$$

The α exponent is usually formally referred to on optics, noted as the "color" of the noise. The white-noise is flat ($\alpha = 0$), the pink-noise has $\alpha = 1$, and other colors are described by various other numbers up to $\alpha = 2$, the brown-noise. The $S(f)$ of pink-noise inversely depends on f frequency, noted as $1/f$ noise. The self-similar processes produce $1/f$(pink) noise covering the time-fractal of life's dynamism [61] [62]. This dynamical fractal structure marks the self-organizing both in structural and time arrangements [63] and dynamically regulates the living matter [64]. The $1/f$ fluctuations [65] define time-fractal structure in a stochastic way of the living systems [66]. The physiological control shows $1/f$ spectrum [67]. One of the most studied such spectra is the heart rate variability (HRV).

Each octave interval (halving or doubling in frequency) carries an equal amount of noise energy in the $1/f$ noise. The self-organized symmetry of living system transforms the white noise to pink [68], forming the most common signal in biological systems [69].

3. Electromagnetic Effect

Biology fundamentally depends on the water. The electromagnetic forces act on various aqueous electrolytes and some solids (like bones) in the systems. The external application of electromagnetic fields on living bodies has four basic categories:

1) displacements of free charges, causing electric current in the system;

2) vibrations of charges in chemical or physical bonds (electrons in atoms, atoms in molecules, surface adhesions, collective-networks);

3) reorientation (torque, rotation, structural change) of dipoles (like water molecules proteins, complex structures);

4) displacement and reorientation of complete cells.

These above effects could make notable changes in the living object:

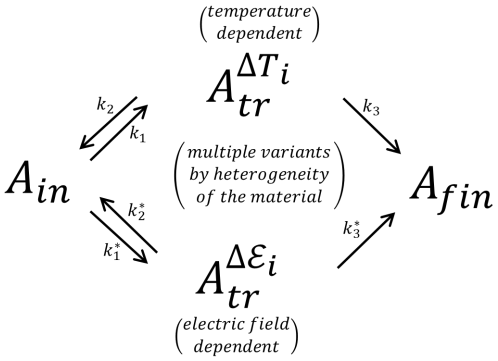
- heat (temperature growth) by energy absorption,
- ignite molecular and systemic excitation,
- modify some suppressor-promoter loops directly by altering the feedback set-point.

These changes could trigger physiologic and biophysical changes of the homeostatic regulation and rearrange of the control. Electromagnetic resonance phenomena attract extensive attention, especially connected to the cells as the integrated carrier and "building blocks" of the living organisms. The Rife resonances appear as a part of these efforts. The critical point is how the electromagnetic forces make an active selection and distort the targeted cells.

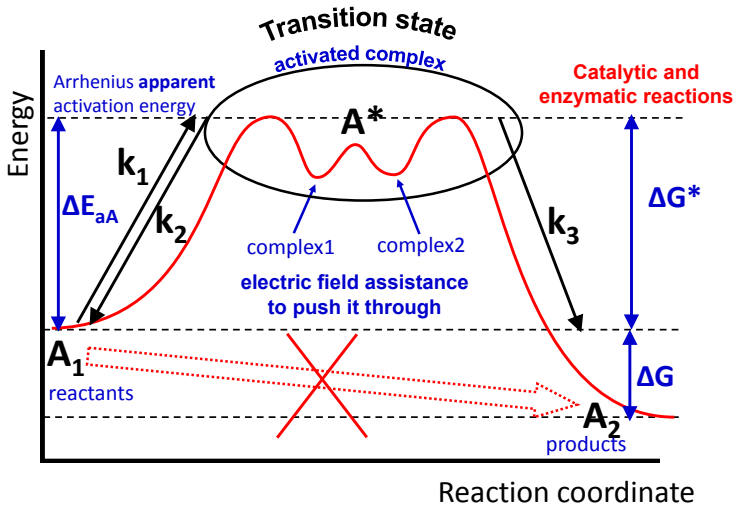
The most trivial connection to how electromagnetism transformed to an obvious direct cellular effector is the heating by energy absorption. When the absorbed energy heats the target homogeneously, we may define the average energy-absorption measurable with the temperature. When the absorption is heterogeneous, the temperature as an average cannot be defined.

The temperature can be replaced by electric fields using their similarities in the absorbed energy [70]. The similarity emphasizes the possibility of the non-temperature changing but due to the energy exchange thermal processes involving the $\sum_i \mathcal{E}_i dP_i$ in the internal energy of electromagnetically heterogeneous media, Figure 1.

Less obvious and more complicated effects are "nonthermal", meaning that the temperature change is not observable. Low-level, non-stationary magnetic fields have been observed [71] and adopted [72] as the nonthermal electromagnetic effect. One of the most important nonthermal processes is the so-called "window" effects [73], having an optimum both frequency and amplitude to interact with cellular membrane [74]. The window effects have some resonance characters. The measured frequency dependence sensitively varies on the experimental conditions and could be in synergy with chemical effects [75]. The



(a)



(b)

Figure 1. The direct transition between A_1 and A_2 is impossible due to the energy barrier. Enzymatic reactions could lower the height of the barrier by a chemical transition state. (a) The electric field-assisted transition works in a similar way, excites the targeted molecules, and forms a transitional state as enzymes do; (b) The transition state A^* is a complex molecular reaction, and the electric field pushes it to the point of no return to finish the transition process.

"window" was measured in multiple power ranges [76], depending on the applied power (amplitude of the signal at the same impedance load), with such small energy, which categorized these experiments definitely as nonthermal. (They used max. 5 μW/g energy). The active Na^+ flux pumping was observed as the maximum between 0.1 - 10 MHz [77], which "window" effect could be well explained by the active transport system model in the membrane [78]. The "window" to increase DNA concentration in the specimen was measured at 10 Hz between 0.03 - 0.06 V/m and 4 - 5 μA/cm^2 electric field and current density, respectively. These low frequencies differ from the Rife-declared ones.

The inherent heterogeneity of the living objects varies the electromagnetic processes in constituting parts of the target. The heterogenic electromagnetic effects sharply divide depending on the aqueous electrolytes or lipid substances (like membranes or adipose cells) or solids (like bones). The actions are frequency-dependent, which form dispersion relations.

Schwan [79] measured the electrical properties of tissue and cell suspension over a broad frequency range. He observed three major frequency dispersions, introduced three dispersion mechanisms (α, β, γ) to characterize the anomalous electric properties of biomaterials. The high heterogeneity of the living tissue differentiation was since low-frequency, radiofrequency, and microwave effects have multiple relaxational processes in their interval [80], **Figure 2**. They are considering different mechanisms at low frequency (α), radio frequency (β), and microwave frequency (γ) processes.

The low frequency (approx. 10 Hz to 10 kHz) α-dispersion. This frequency-range acts mainly in muscle tissue [81], and so it is connected to the tubular system [82]. The vanishing of the α-dispersion frequencies indicates first the dying process of the tissue [83].

The β-dispersion is superimposed to the high-frequency end of α-dispersion. It has a link to the cellular structure of biological materials [84]. The β-dispersion occurs at the interface of membrane-electrolyte structures, using Maxwell-Wagner

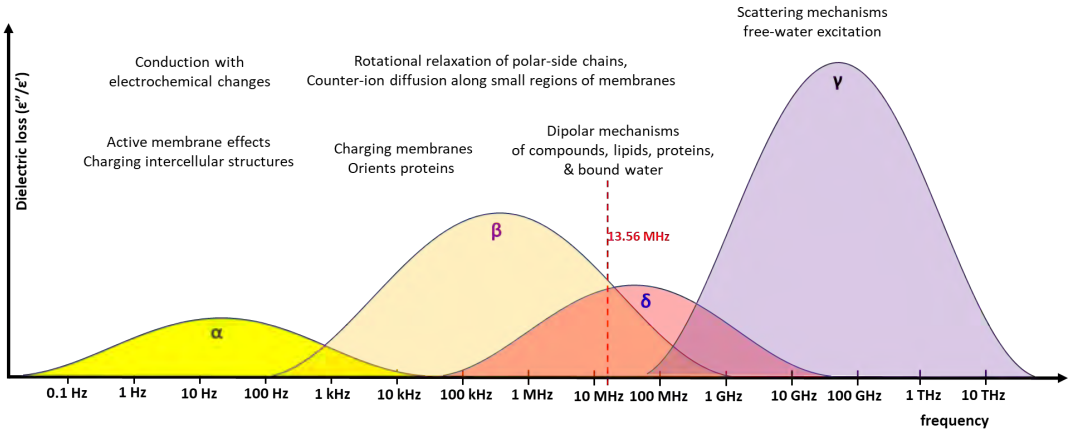


Figure 2. The various frequency intervals of the dispersion phenomena. The overlapping of β and intermediate band between β and γ form a biologically important range. The protein-lipid interaction and the bound water could react in this frequency interval.

relaxation [85]. Interfacial polarization of the cell membranes appears in this frequency range [86], connected to the charge distribution at the cellular of interfacial boundaries [87].

The upper tail of the β-dispersion continues to the δ-dispersion [88]. The dipolar moments of proteins and other large molecules (like cellular organelles, biopolymers) cause this frequency spectrum [89]. This second Maxwell-Wagner dispersion (δ) also depends on the suspended particles surrounded by cells [90], as well as the protein-bound water, and cell organelles such as mitochondria [91] [92] appear in the range. Furthermore, other relaxation processes like molecular side chains, bound water molecules, diffusion of charged molecules, and near membrane bounds change the δ-dispersion. The most frequently used ISM-frequency (spectrum reserved internationally for industrial, scientific, and medical use) is 13.56 MHz in the overlapped region β- and δ-dispersion range. The model calculation also shows the importance of the 13.56 MHz [93].

The plentiful tissue water causes the high-frequency dispersion (γ) at microwave frequencies [94]. The excitation of various electrolytes' water content in the cytoplasm and extracellular matrix (ECM) is responsible for this high-frequency end. The time constant is proportional to the third power of the molecules' radius, and typical characteristic frequencies are, e.g., 15 - 20 GHz for associated with the polarization of water molecules and 400 - 500 MHz for simple amino acids. The gamma range locates the molecular resonance of proteins [95].

The dispersion effects overlap and depend on the target material and their environmental connections, so the electromagnetic fields could influence many parts simultaneously, even with constant frequency.

4. Challenge of Resonant Energy-Absorption

The resonances appear in various thermal, electrical, and mechanical properties of the cells, tissues, and organs. The well-tuned resonance minimizes the energy loss during its transfer, which is in harmony with nature's general thermodynamic rules. The application of the resonance phenomena for the living systems has two fundamental challenges:

Which mechanism transfers the resonant energy to the cells?

How can the cancer cells be selected to be destroyed by resonance, and how is it harmless for healthy cells?

Rife's original idea initialized the resonant phenomena to eliminate the "unhealthy living cells" with the frequencies used for cellular resonances around kHz. The energies of these waves (in order of pico eV) are certainly less than the temperature background's thermal energy ~300 K of the human body (250 meV). His experiments were completed in vitro on cell cultures, where the challenge of selection does not appear; all cells were malignant. His observations did not give any clue for the energy transfer mechanism, and the MOR investigation misses the statistical evaluation. Only the visually observed cell distortion was measured; no other parameters are available. So, these early observations were

indicative only.

4.1. Deterministic Resonance

Rife declared a mechanical "blow up" of the cellular structures, investigating in vitro. The cavity may work as a resonator which could cause resonant energy absorption. There are plenty of cavities by a membrane with surfaces of lipid-constructed boundaries like cells, mitochondria, intracellular organelles (like tubes of tubulin, and various intracellular structures with cavities). However, cavity resonance would require a wavelength comparable to its size. The mechanical effect depends on the size and the actual form of the cells, which are well unified in bacteria culture but not unified in a tumor, where heterogeneity is a fundamental inherent behavior. The Rife frequencies' wavelengths are many magnitudes longer than the cell sizes, so the direct mechanical cavity resonance does not fit.

Additionally to the heterogenic form of the cellular cavities of malignancy, their electromagnetic and mechanical parameters (like dielectric constant, conductivity, density) change by their present activity depending on their functions in the system's structure. Other resonance possibilities are represented by the different molecules, including the water. These molecular components have notable resonance bands, but their frequencies are too high to compare them to Rife declarations.

A kind of mechanical resonance induced by ultrasound could exist [96] in the kHz-MHz region [97]. It could select the cancer cells [98], because they are softer than their healthy counterparts [99] [100], so the waves could interfere with the soft and individual cells. Nonthermal cellular resonant mechanisms which convert electromagnetic radiation to such mechanical frequency have no proof yet.

One of the most proven resonance phenomena in living objects is the ion cyclotron resonance (ICR). The method has strong theoretical [101] [102], and experimental pieces of evidence [103]. We shall assume a long impact time at ionic cyclotron resonance so that the trajectories should form and endure for a long time. However, the ICR and the connected phenomena need a magnetic field's assistance, and the resonances happen in low frequencies, on the order of a few times ten Hz. This does not fit to Rife's assumptions.

4.2. Stochastic Resonance

A mixture of deterministic signals and noise could produce stochastic resonance output in a nonlinear system. Its autocorrelation function $R_{XX}(t_1, t_2)$ or power density spectrum $S(f)$ could characterize the output noise.

One of the origins of the stochastic (probability) behavior of the living matter is the intrinsic bifurcation in all the levels of the living organization [104]. The basic bifurcation mechanism could be introduced by a simple nonlinearity of the potential wells of chemical reactions [105] [106] showing nonlinear behavior by

double-well potential (non-harmonic potential, chaotic arrangement). The simplest bifurcative phenomenon is when the active forces $F_a(x)$ are not linear with the displacements x (or generally with the deformations):

$$F_a(x) = ax + bx^3 \tag{2}$$

where a and b are characteristic parameters of the interaction. The potential energy $E_{pot}(x)$ of this force

$$E_{pot}(x) = ax^2 + bx^4 \tag{3}$$

which shows the bifurcative double potential well when $a < 0$ and $b > 0$. This potential offers equal probability for the particle involved in the $F_a(x)$ being in both wells, so the particle bifurcates between the two positions x_1 and x_2 Figure 3. There are particles in the potential valleys that perform a harmonic oscillation. The noise constrains the particle to oscillate between the wells randomly.

An additional factor cx^3 to (3) breaks the equal probability, Figure 4, and the bifurcation (or multifurcation), the probability distribution biases the jumps.

The system's noise adds an anharmonic factor to the potential, so the wells' equivalence disappears. The change modifies the optimal energy situation and constrains the bifurcation, which could direct the particle movement in the series of jumps into one direction. The noise modifies the depth of the wells. When the force is periodical, the wells periodically fluctuate accordingly up and down in opposite directions. When the amplitude A of periodic force is small to compare $\Delta E_{pot}(x)$ the equality of the two wells of the potential periodically is oppositely broken, but in a long-time average remains equal (Figure 5).

At the start in the time $t = 0$ the jump from right to left is more probable than a half period later, at time $t = \pi/2\Omega$, and opposite in the time of $t = \pi/\Omega$.

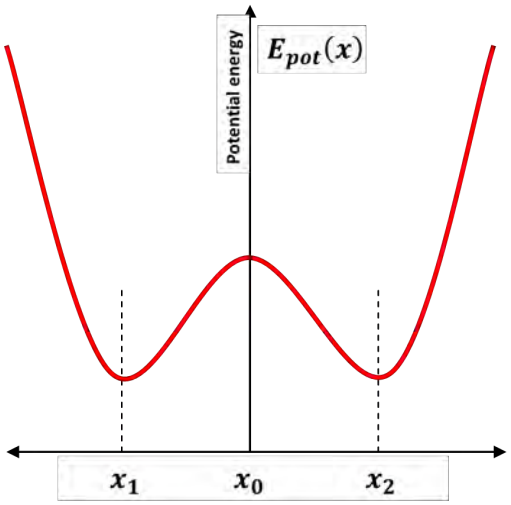


Figure 3. The bistable potential-well. The system has two stable positions (two energy minima), and it is in dynamic equilibrium when the two states are occupied with equal probability by oscillation. When one state becomes fixed in one well, the system is "frozen", the equilibrium is broken.

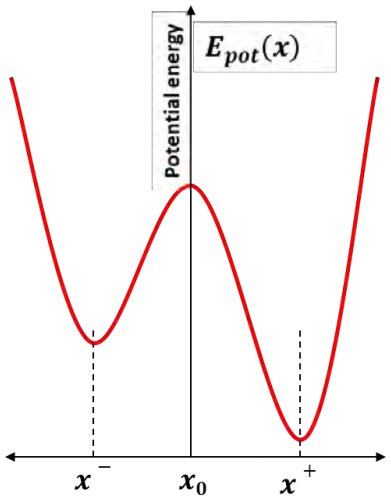


Figure 4. The characterization parameters of the unbalanced bistable potential-well, $E'_{pot}(x) = ax^2 + cx^3 + bx^4$, ($a < 0, b > 0, c > 0$). The oscillation is unbalanced, the probability being in the well at x^+ is higher than at x^-.

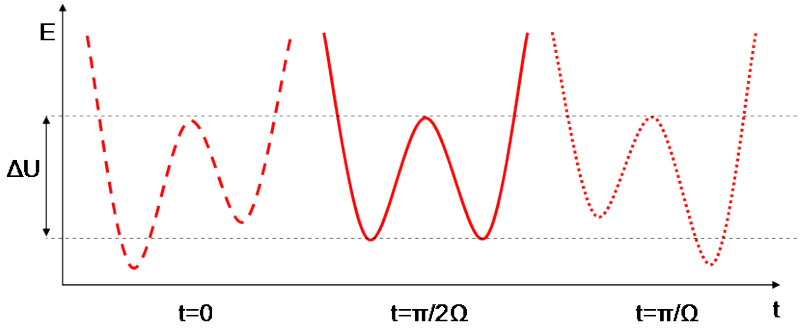


Figure 5. Changes of the bistable potential-well by elapsed time (one time period of the exciting signal is $T = 2\pi/\Omega$, where $\Omega = 2\pi f$ is the conventionally used circular frequency).

In this way, the weak periodic signal compared to the activation energy $\Delta E_{pot}(x)$ synchronizes the jumps in a stochastic (not deterministic) way. Consequently, the jumping time's distribution function through the barrier from the potential well in the noise, which is modulated with a weak periodic signal, will not be rigorously monotonic. A considerable amplification of the weak periodic signal could be observed depending on the strength of the noise. The amplification also increases by the decreasing frequencies at a constant amplitude of the periodic carrying signal. The amplification also increases by the decreasing amplitude of the periodic carrier on the same signal frequency, and suddenly (at a threshold), the resonance disappears (window phenomenon). Probably this is the reason for the observed Adey-window, [77]; and some other detected resonance phenomena with an application of outside periodic electric field.

The resonance-like maximum depends on D noise energy or at $D = const.$ the frequency determines the maximum. This is the typical frequency-amplitude window formulated before the experiments [84]. The amplitude has a reson-

ance-like behavior, Figure 6. White noise induces the resonance when $D = k_B T$ (thermal noise) and so the noise intensity is temperature dependent.

A particularly notable application of this stochastic resonance is the possibility of using electrically generated subthreshold stimuli in various biological processes [107]. The stochastic resonance works, and it remains a vivid possibility to explain Rife frequencies. The entry of a molecule to the cell through gating membrane channels has Poisson distribution in the stochastic resonance study for single-cell [108]. The response to very weak external electric fields could be far below the thermal noise limit. We had shown for zero-order of the noise that thermal limitation does not exist [109].

4.3. Enzymatic Resonance

Enzymatic assistance boost most of the chemical reactions in living processes. The cellular machinery requests various and numerous catalytic reactions. The living systems have tremendous enzymatic processes (so-called "catalytic wheels" [110]). The wheels model describes a cyclic catalytic reaction having two conformation states of the enzyme governing the actual process's speed. This classical model (Michaelis-Menten enzyme model, [111], MME) well describes the enzymatic procedures steady-state [112]. The simple mathematical description involves an enzyme (E) starting the formation of the product (P) from a substrate material (S) through a transition state (E^*):

$$E + S \underset{C_{rev}}{\overset{C_{forv}}{\rightleftarrows}} E^* \xrightarrow{C_{fin}} A + P \tag{5}$$

where the reaction rates characterize the reverse, forward, and final conversions (C_{rev}, C_{forv} and C_{fin}), respectively. At first, the enzyme in conformal state E connected to S substrate state and form E^* complex: $E + S \to E^*$. The E^* state is highly complex because it has two 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, Figure 7.

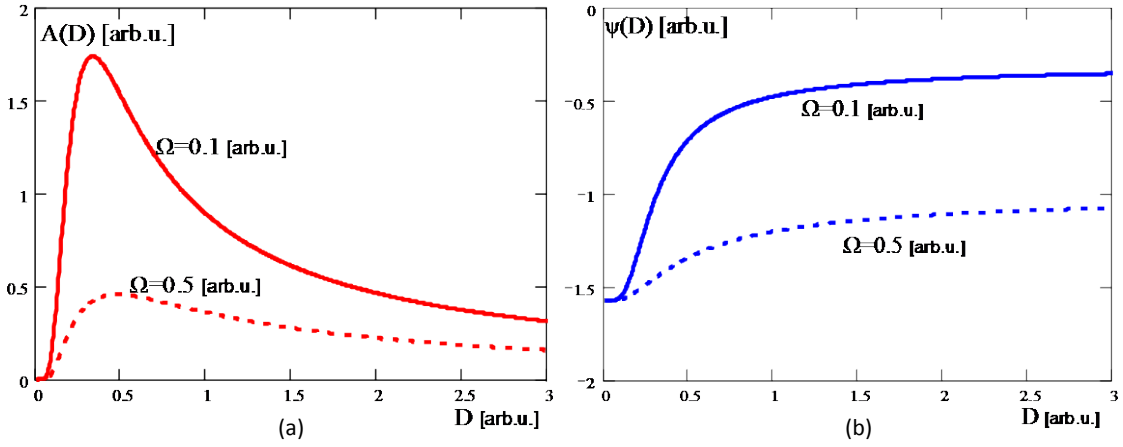


Figure 6. The stochastic resonance depends on the noise-density D. (a) Amplitude $A(D)$; (b) Phase-shift $\psi(D)$ of the noisy carrier. The resonance depends on $\Omega = 2\pi f$ circular frequency in stochastic processes.

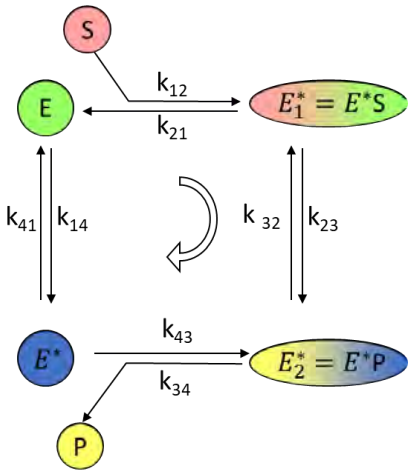


Figure 7. The enzymatic "wheel". In practice $k_{14} < k_{41}$, $k_{21} < k_{12}$, $k_{32} < k_{23}$ and $k_{43} < k_{34}$, so the "wheel" works in one direction, by Michaelis-Menten process.

To understand the complex enzymatic transition state, let us assume two certainly distinguishable confirmation state of an actual enzymatic reaction: E_1^* and E_2^*, with concentrations $\left[E_1^*\right]$ and $\left[E_2^*\right]$, respectively. These two states are the result of chemical reactions, hence

$$E_1^* \underset{\beta=k_{32}}{\overset{\alpha=k_{23}}{\rightleftarrows}} E_2^* \tag{6}$$

An external electric field could modify the catalytic/enzymatic wheel. This process is the electro-conformational coupling (ECC, [113] [114]), it activates the energy over the barrier by oscillatory stimulation [115]. The outside periodic field modifies the activation energies with $\Omega = 2\pi f$ circular frequency. Stochastic resonance determines the final catalysed state's probability in the dynamic equilibrium of homeostasis [116]. The thermal white noise energy $D = k_B T$, pumps the resonance, so enzymes get the energy from the environmental conditions. Significantly the lower frequencies (smaller Ω) increase the resonant peak, but the effect vanishes at the too low frequency when the acting noise washes out the signal. This threshold depends on the processes and conditions when the process is applied. The optimal (peak) resonance depends on the D noise-density. Due to the thermal noise depends on the temperature. Consequently, the excitation process has an optimal temperature, but the temperature dependence less effective when a colored noise forces the resonance.

The number of resonance frequencies as many as catalytic reactions exist. It is a large number indeed. All cells have mostly identical enzymatic reactions, hindering the selection of cancer cells by stochastic resonances. All small amplitude modulation with the carrier stochastic resonance frequency makes certain resonant effects with enzymatic processes but also excites other two-state situations (like voltage-gated ionic channels), which further complicates the selection. Due to the ordered reaction lines in cellular processes, the microscopic effects have a macroscopic result when the autocorrelation of the excitatory signal forces the

order of the signal pathway in the cell. Consequently, the selection of malignant cells could be possible by well-chosen signal modulation, a time-set of frequencies, and not only a single one.

A weak periodic perturbation promotes transport activities by stochastic resonance near the membrane. The thermal noise plays a vital role in pumping the energy to this process by Brownian engine [117] [118]. The enzymatic resonance fundamentally depends on the thermal conditions of the tumor and cellular microenvironment, the extracellular matrix. The thermal noise activates the Brownian motor, which drives the enzymatic wheel. The ECC situation rectifies the thermal fluctuations, producing directed motion in one direction only [119] [120]; forming a "ratchet", excluding the swivel's opposite turn. The free energy can be obtained from the inherent fluctuations and outside electric noises [121], by the stochastic concept. The "ratchet" idea was originally proposed by Feynman [122], but it was incomplete and cleared later [123]. The ECC realizes a direct coupling between the outside electric field and the enzymatic processes at the membrane. The alternating electric field impacts enzyme activity [124] and modifies the extrinsic signal-transduction [125].

The stochastic resonance excites any catalytic wheel reaction or voltage-controlled ion channel. Consequently, shifting of the ionic composition and pH could destroy the microbes. However, the stochastic resonance has frequency windows. Below and over an amplitude or noise energy, it does not work. Subsequently, in principle, the explanation of the resonant frequencies measured by Rife and others is possible, or at least it is not excluded in this way, but as numerous as enzymatic reactions exist in the system. This involves a dense spectrum of resonances, and the real destroying process needs a set of resonances that are adequate to the signal-transduction line in the cells. With these resonances, we do not expect prompt necrotic cell-death.

The stochastic resonance may amplify the signals. In a simple model, the wheel is energized by ATP hydrolysis with 10-16-10-17 W, while the molecular scattering due to the thermal effects provides 10-8 W [126]. The stochastic resonance conditions promote the ATP hydrolysis as a periodic process, producing the given reaction's direct stimulation. The same could happen by excitation with a periodic outside field using the EEC effect and supporting the stochastic resonance. However, the fluctuation-driven directional flow described by ECC needs more effort to clear the ion-pump processes in detail [127].

An appropriate regularly oscillating electric field may convert the free energy-producing transports or chemical reactions coupled through enzymatic processes [123]. The translational symmetry can be broken in one direction by the periodic signal superimposed on the double-well symmetric enzyme-potential, **Figure 8**. A Brownian motor drives this process, enforced by an electric field pushing through the ligand on the membrane from one side to the other, differs from the MME.

These processes excellently demonstrate the irreversible thermodynamics in the presence of an external periodic perturbation [128]. The transduction of

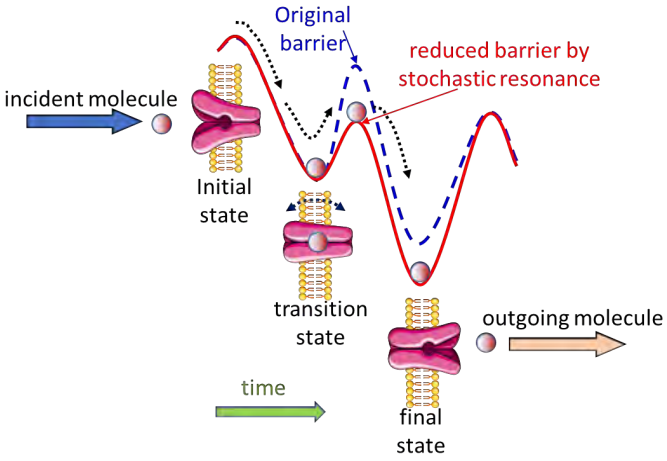


Figure 8. Stochastic resonance promotes the ion transfer through the membrane.

low-level signals can be resonant [117], acting on the enzyme's oscillating barrier involved in the studied reaction. The energy barrier of APT→ADP reaction is $\approx 30 k_B T$ and the maximal energy oscillation by the external field is $\sim 2.5 k_B T$. This oscillatory activation was observed as low as $5\ \text{mV/cm} = 5\times 10^{-7}\ \text{mV/nm}$ with AC (10 kHz). The reactions involve a synergy of the enzyme with excitation with extremely low levels of electromagnetic fields.

4.4. Collective Excitations

The living system has chain reactions (like the Krebs cycle) using the transient states to go over the energy barriers' sequences. The Brownian-ratchet might be involved in all the barriers, reducing the height of the barrier by ECC pumped by environmental noise, **Figure 9**. The reactions follow Markovian sequences and develop conditions for the next step of the series in the chain. The various steps have different energy consumption and chemical reaction rates, far from a simple staircase process. The well-definite set of the chain fixes a certain time-series required by the setting of the ongoing reactions. The characteristic time-sets appear in the time lag of the measured signals' autocorrelation function.

The reaction avalanche on this way has an energy-wave "sliding" through the chain, energized by the ATP→ADP conversion and promoted by the ECC process. One form of the sliding energy-bag through a system is the biosolitons [129] [130]. The solitons (solitary waves) maintain their shape by self-reinforcing wave packets (energy-bags) propagating constant velocity. The dispersion in nonlinear conditions produces permanent and localized waveforms in a region. The solitons remain unchanged by their mutual interactions, only their phase-shift changes. The energy-transfer by solitons has negligible energy loss [131]. One of the most practical simple soliton presentations led to its discovery, seeing a bump-shaped sliding single wave of water through a canal. The sliding energy bag is easily presented with a falling domino-row when the actual energy outside the energy source (the gravitation) subsequently plunges the single dominos in the row, and a wave runs with unchanged shape generating energy delivery. The

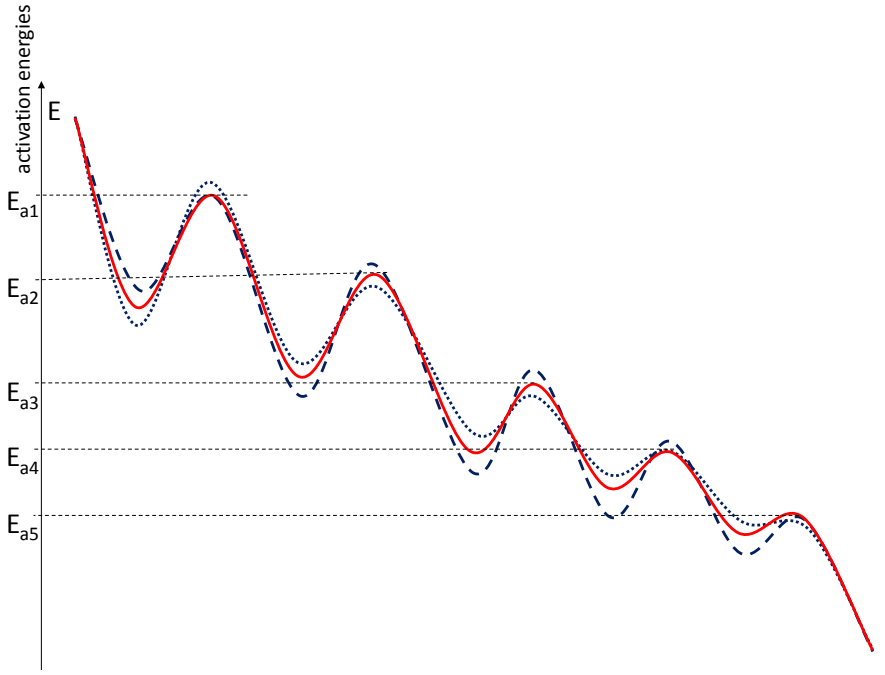


Figure 9. Cascade of activation energies. Time series of sequentially happening reactions going over the actual activation energy. The well chosen autocorrelation time-lag promotes this series.

phenomenon is collective [132] and has broad applicability in neuron signal propagation [133], and has a role of membrane dynamics [134]. Excitation of individual large complex molecules like DNA [135] and proteins [136] also show collectivity. The thermal noise background influences the solitons, but the biosolitons are stable in the living temperature range [137] [138].

The formation and decay of solitons explain the unidirectional enzymatic cycle of ECC [139]. In molecular chains triggered by periodic external electromagnetic fields, solitons create a ratchet directed [140], sliding stability bag, **Figure 10**. The experiments show soliton-coupling of K^+, Na^+, Rb^+ through membranes [124] [141] [142].

The nonlinear, systemic collective harmony of macroscopic phenomena characterizes the biosolitons. The collectivity driven by the energy-transfer is well shown in large molecules like alpha-helix of proteins [143] in THz frequency region but also appears mass-movement at lower frequencies [144]. The soliton harmonization of the collective movements emerges when the cells starve and need collective efforts to survive, sharing the available energy as optimally as possible [145].

The hydrogen ion can be transported by the hydrogen bridges, which is crucial in living systems [146]. The Grotthuss-mechanism describes the high-speed and low dissipation of the transport propagation [147] [148]. Here the proton tunnels (jumps) from one water cluster to another bridged by hydrogen bonds, **Figure 11**. A "frustrated bifurcative" proton dynamically connects the neighboring water molecules, producing a chain reaction.

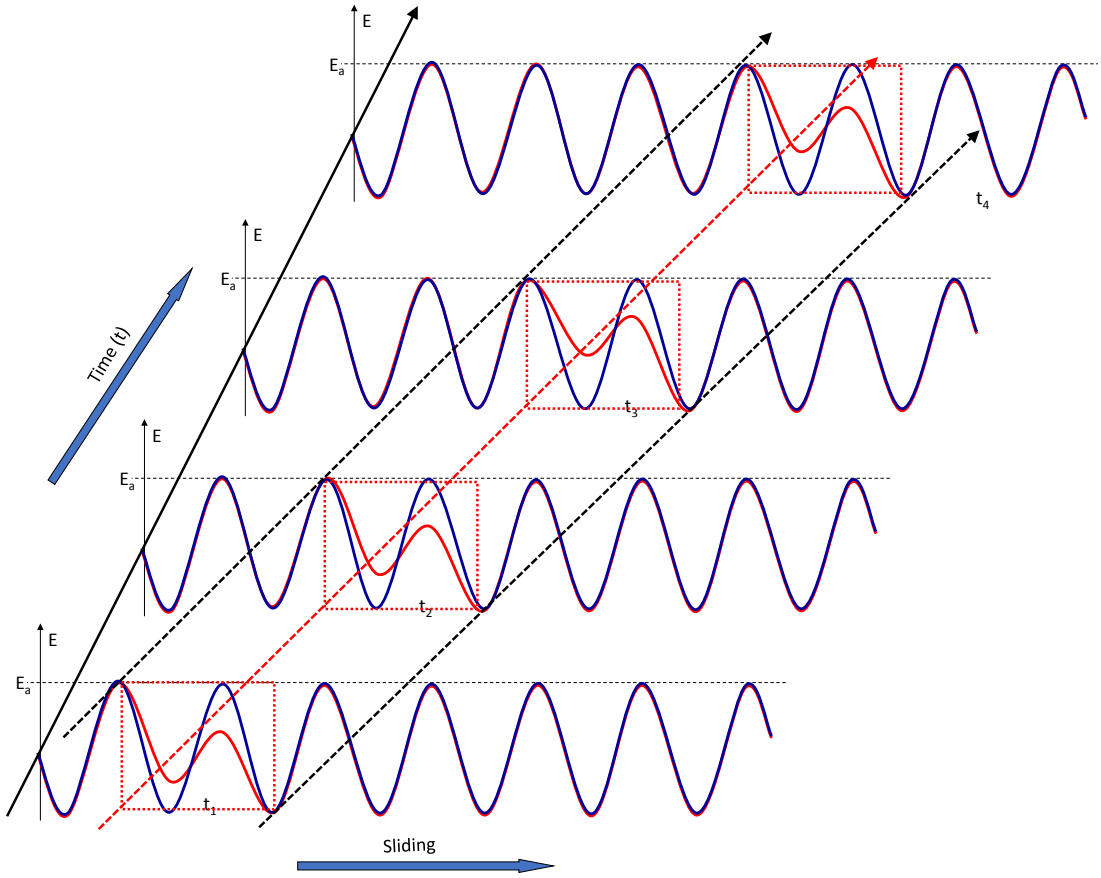


Figure 10. The "siding" bistability by the enzymatic processes.

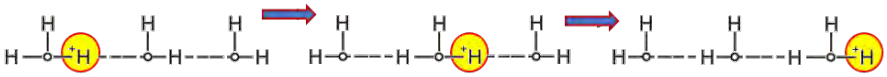


Figure 11. The Grotthuss mechanism of proton-jumping in a chain. (Three subsequent steps of the process are shown.)

$$H_2O + H_2O \rightleftharpoons OH^- + H_3O^+ \tag{6}$$

The lifetime of H_3O^+ (hydronium ion) in (7) is relatively small (~3×10^{-12} s) so the speed of proton transport by Grotthuss-mechanism is approximately ten times higher than the diffusion, so it is decisional. The Grotthuss-mechanism propagates the ionizing chain of a water molecule. The dissociation and recombination steps are altering in the "traveling". The recombination-dissipation is a quantum-mechanical process, in principle almost free of dissipation [149]. The process works like quantum wiring [150], having temperature dependence. The vector potential can modify the quantum-states of the water [151] [152] [153], which could modify the complete chain processes. The water order selects between the ionic flows preferring the proton against all the other reaction-product. The outside electric field's effect could conduct the hydroxyl (OH^-) and hydronium (H_3O^+) ions by the same Grotthuss mechanism going through the chain like a stability bag.

4.5. Modulation of the Electromagnetic Signal

The concept of modulation is centered on the stochastic dynamics (time-dependent events) in the biosystems. The chosen frequency spectrum is devoted to direct actions promoting healthy controls and suppressing the cancerous processes. The carrier frequency is in the RF range, which delivers an audio range (<20 kHz) to the place of use, Figure 12.

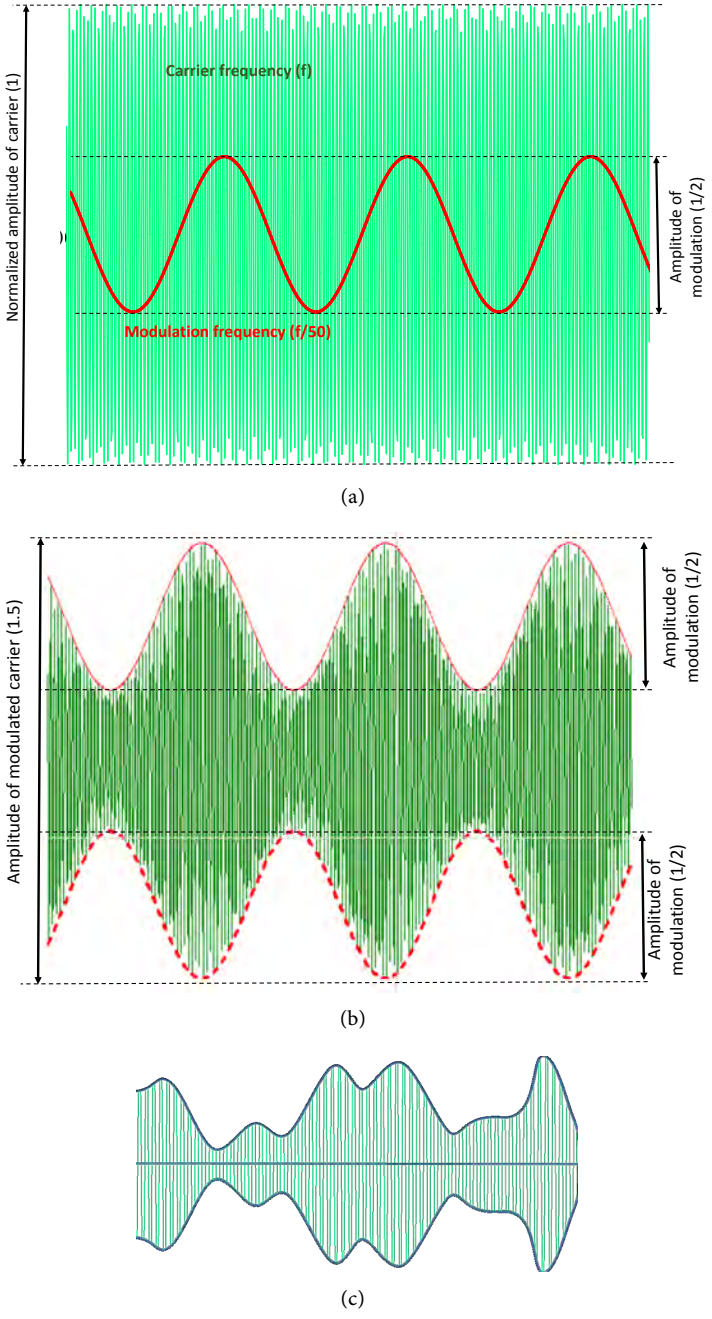


Figure 12. The modulation. (a) The high carrier frequency (green) modulated with the periodic low-frequency signal; (b) The modulated signal shows the importance of the much higher frequency of carrier than the carried modulation; due to follow the shape point-by-point; (c) Modulated transmission of a non-periodic signal.

The expected actions mark out the following basic goals:

1) Support the healthy network against the out-network, autonomic cells in the selected target.

2) Support the immune system, boost the homeostatic chains of reactions.

3) Excite the selected molecules in cancer cells for particular damage-associated molecular patterns (DAMP) and immunogenic cell death.

Due to the complex interconnection of the living objects, these effects overlap and support each other. The question naturally arises: when the modulation frequencies have such an advantage, why does the complication with carrier frequency be involved, and why not applied the modulation frequency directly, without a carrier? Deliver the low frequency into the body and focus it on the selected places is a challenging issue. The adipose tissue in the skin layer, the various membranes, and isolation compartments block the low-frequency penetration deeply into the body. The electric impedance of these heterogenic isolating (capacitive) factors inversely depends on the frequency. This resistivity became too high in low frequencies, and no deep targeting is possible. Invasive application may surmount the adipose layer, but the electrochemical Warburg impedance [154] [155] is high in low frequencies, preventing penetration. The proper solution of the deep penetration needs a high frequency in β/δ-dispersion range. The modulation of a high-frequency carrier with a low frequency solves the apparent contradiction. The well-chosen carrier makes the selection of excitations, and the low-frequency modulation excites. The advantage of the energy absorption compared to conventional heating has significant approval [156].

4.6. Demodulation of Electromagnetic Signal

Theoretical [157] and experimental researches [158] show that at high frequencies only thermal energy-dissipation happen. Low frequency is requested for electric excitation of molecules ("nonthermal" effects). The signal needs demodulation, separate the low-frequency from the carrier. The demodulation is a rectification process, which extracts the information from the carrier wave.

The cells demodulate the received signal by two ways:

- normal rectification by the highly polarized cell-membrane, [159] [160] [161]
- stochastic resonance makes the rectification, [162].

The existence of nonlinearity in cellular biological objects had intensive research, but at the beginning, only linear attenuation of the amplitude of the alternating current through the living object was measured. The double membrane effect causes this apparent linearity, **Figure 13**.

The excitation process acts on the transmembrane proteins, so the single membrane demodulation perfectly satisfies the demands. The nonlinearity through the membrane can be measured [163], and the harmonics make dissipative terms [164].

The noise threshold complicates the rectification of the applied signal. In principle, the modulated signal must be larger than the thermal noise. The requested

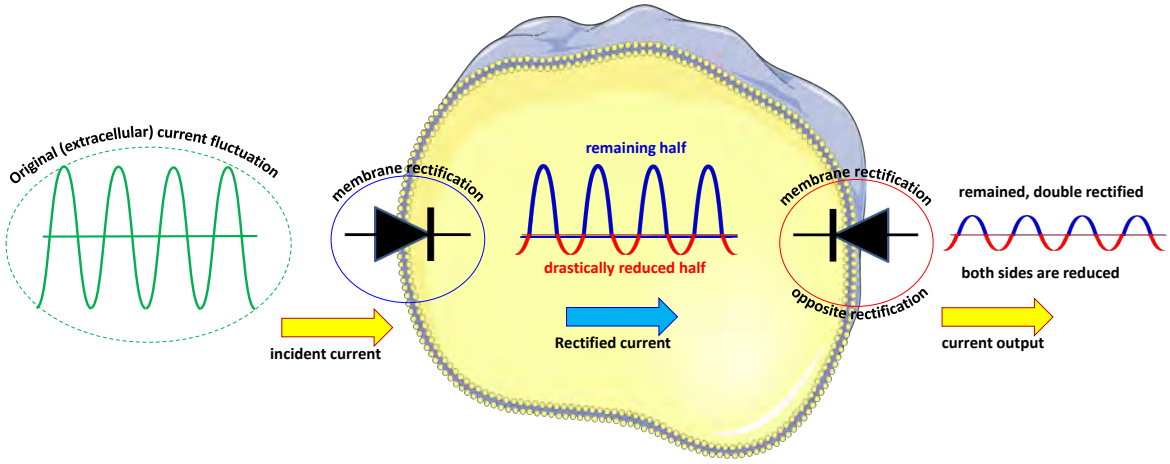


Figure 13. The symmetric but opposite rectification of the cell-membrane when the current goes through the cell makes the measured material linear, the rectification disappears. (The ⊣▶⊢ sign symbolizes the rectifier (diode).)

signal intensity would have such high electric field, which impossible to apply in the living system without fatal damage. In the early model it had been shown this strict thermal noise limit at low frequencies [165], but in a revision it had been shown that the zero mode currents have no thermal limit of the electric rectification [109]. The low frequency (the $1/f$ signal) of the AM modulation is intensively active in its demodulated form [166]. The demodulation of the AM modulated signal by stochastic process is an option too [167], which is applicable also for other forms of modulation [168].

4.7. Excitation Processes

The special autonomy and high metabolic activity of the malignant cells allow their recognition and selection, and attack. In consequence of the higher metabolic rate of malignant cells than their normal hosts, the microenvironment's electric conductivity grows for a detectable range. Furthermore, malignant cells' autonomic behavior rearranges the microstructure of the ECM, which changes their dielectric permittivity [169] [170], and the order-disorder transition of the aqueous electrolyte also has a role in the changes [171]. The conductivity and permittivity allow the selection of these cells [172]. The amplitude modulation intensifies the tumor-specific energy absorption as a part of the selection mechanism [173]. The electromagnetic selection of the malignant cells guides the energy delivery. The small energy absorption could cause damages in the cytosol [174], or trigger apoptotic signals and destroy the cell [175]. The nonthermal processes result from the change of the chemical or structural situation in the targeted assembly [176]. The transition does not use heat from the field but directly uses the electric field's work for the actual changes by absorption. Besides, the β/δ-dispersion of the carrier frequency orients the attack on the membrane reaction of the impedance selected cells [177] [178], primarily for the transmembrane groups (rafts) of proteins [179]. The rafts of the plasma-membrane of malignant cells are denser in rafts than their healthy counterparts [180], allowing

intensive excitation of the transmembrane proteins [181]. A new kind of treatment applies to these facilities [182].

4.7.1. Boost the Healthy Network

The malignant development avoids the healthy homeostatic regulation, "defrauds" the controls for their intensive, unhealthy proliferation. Cancer, in general, is the missing of homeostatic control over malignant cells. The cancerous lesions develop the strength to proliferate as intensively as possible, ignoring the healthy regulations and exploiting the host tissue's collectivity. The proliferation subordinates all malignant features. The cancer cells became gradually autonomic, break the connections. Here is their weakness: the cancer cells are individual and not networked like the regulated healthy host. Their collectivity satisfies the individual demands to use energy as much as possible for the cellular division.

The modulation frequency spectrum follows the natural dynamism of the $1/f$ time-fractal fluctuations and forces to reestablish the harmony with the homeostatic collective network. Simply speaking, the modulation acts in harmony with the natural collective processes, promoting them, like keeping the swing in move using harmonic push, Figure 14.

4.7.2. Support the Immune System

Homeostatic dynamic equilibrium is too complex for external constraints to be effective in repairing it. Tightly connected feedback mechanisms regulate the system, and the reaction of homeostatic control will be against any simple constraints. Consequently, any winning strategy must work in conjunction with homeostatic controls, utilizing natural processes and supporting the immune system to recognize and destroy malignant cells throughout the body. The immune system's preparation could be a perfect target instead of cancer's main strength, its proliferation. The lack of adaptive immunity to tumors can be revised and form tumor-specific immune action to eliminate the malignancy in healthy regulation by the host system itself.

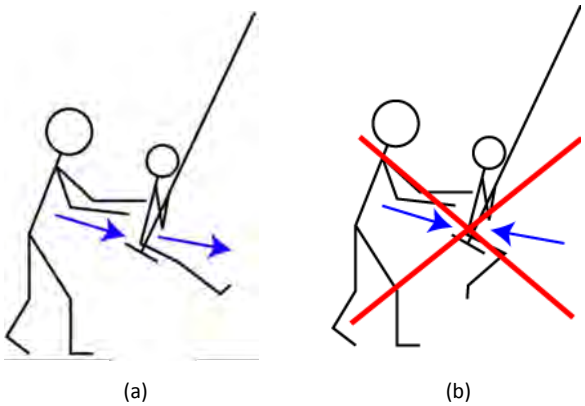


Figure 14. A simple swing example of harmonic and non-harmonic excitation. (a) The swing is harmonically (resonantly) pushed, the energy transfer is optimal; (b) In case of an unharmonic push, the system does not follow the resonant rules. The efficacy is low with tremendous efficacy loss.

Numerous variants aim to activate personal immune defenses against cancer. The key point of these is the immunological recognition of the malignancy. The immune system needs recognizable signs to direct its actions. However, the highly adaptive hiding strategy of malignant cells protects them from being identified by immune cells. The innate antitumor immune action of NK cells [183] [184] offers one of the effective possibilities against cancer invasion. NK does not need information through the host's MCH-I molecules and also acts in the absence of priming. The cytotoxic activity of NK potentially controls tumor growth [185]. Intensive low-frequency components in the modulated treatment spectrum may trigger the NK activity and enrich NK cells in the targeted, selected tumor [186].

The modulation also effectively supports the healthy adaptive immune effects with tumor-specific CD8+ killer T-cells. The destruction of the malignant cells is dominantly apoptotic by the signal excitations of modulated RF-current [187], developing damage-associated molecular pattern (DAMP); as important genetic information for the immunogenic cell-death (ICD) [188] [189]. Immune-stimulators, which have no anticancer effects alone, have synergy with the modulated field. One in vivo study showed the synergy with a herb extract from Marsdenia tenacissima (MTE), producing systemic effects from local application of modulated field [190]. With dendritic cell (DC) inoculation to mouse, which anyway does not cause antitumor effect, the field application showed a significant effect of immune reactions, measured the high value of tumor-specific adaptive response [191]. The DC addition not only effectively develops tumor-specific killer and helper T-cells but also works like a vaccination against the rechallenging of the same tumor to the previously cured animal [192]. Significantly the additional administering dendritic cells may boost the overall immune effects, and also, independent immune-stimulator work in harmony with modulated treatment. In this way, the local treatment became a systemic fight with the malignancy in the entire body [193] [194]. The clinical applications well correspond with preclinical experiments, had shown the same results, using other synergic immune-stimuli [195] [196]. Recent reviews of preclinical [197] and clinical results [198] show efficacy in oncology of this bioelectrodynamical resonant approach.

5. Conclusions

The modulated electric field is an emerging new direction of cancer therapies [154]. The treatment uses stochastic processes, including resonances, "nonthermal" effects, and collective excitations. It could selectively deliver energy to the tumor cells to ignite antitumor-effect by producing DAMP and ICD and liberating the malignant cells' genetic information. The remarkable advantage of this method is that no ex-vivo laboratory manipulation is necessary for the perfect antigen production and cellular reactions.

The proper electromagnetic resonance therapy adopts the natural heterogeneity

of the dynamic properties of the living system. The modulated field application chooses a new paradigm of resonances: it heats heterogeneously instead of the homogenous (isothermal) approach of conventional hyperthermia. The selection uses the tumor, malignant cells' thermal, and electromagnetic behaviors. The heterogeneity is presented by cell-specific electric conductivity, dielectric permittivity, the structural differences of the cell membranes, and the variation of the cooperative harmony of the malignancy. The natural heterogeneity allows producing a synergy of electric and thermal processes [199]. The specialization operates with precise electromagnetic impedance selection [200], using the heat on membrane rafts [201], and makes harmony by thermal and nonthermal effects, too [202].

The structural and time fractals of the living organisms with malignancies offer a special use of fractal physiology. The applied time-fractal amplitude-modulated RF carrier frequency forces proper healthy resonance utilizing the homeostasis's dynamism is followed and modified by time-fractals. A collective resonance occurs, exciting the biosolitons in large molecules. The $1/f$ modulation approach differs from the direct resonance, acting on the collective harmony, setting harmony within the reactions by the modulated signal's autocorrelation. The resonances mostly happen in a stochastic way, modifying the enzymatic processes. A large number of enzymatic reactions fit the stochastic resonance frequencies. Consequently, the number of resonant frequencies is as many as the enzymatic reactions in the target.

The above considerations allowed to develop new method called modulated

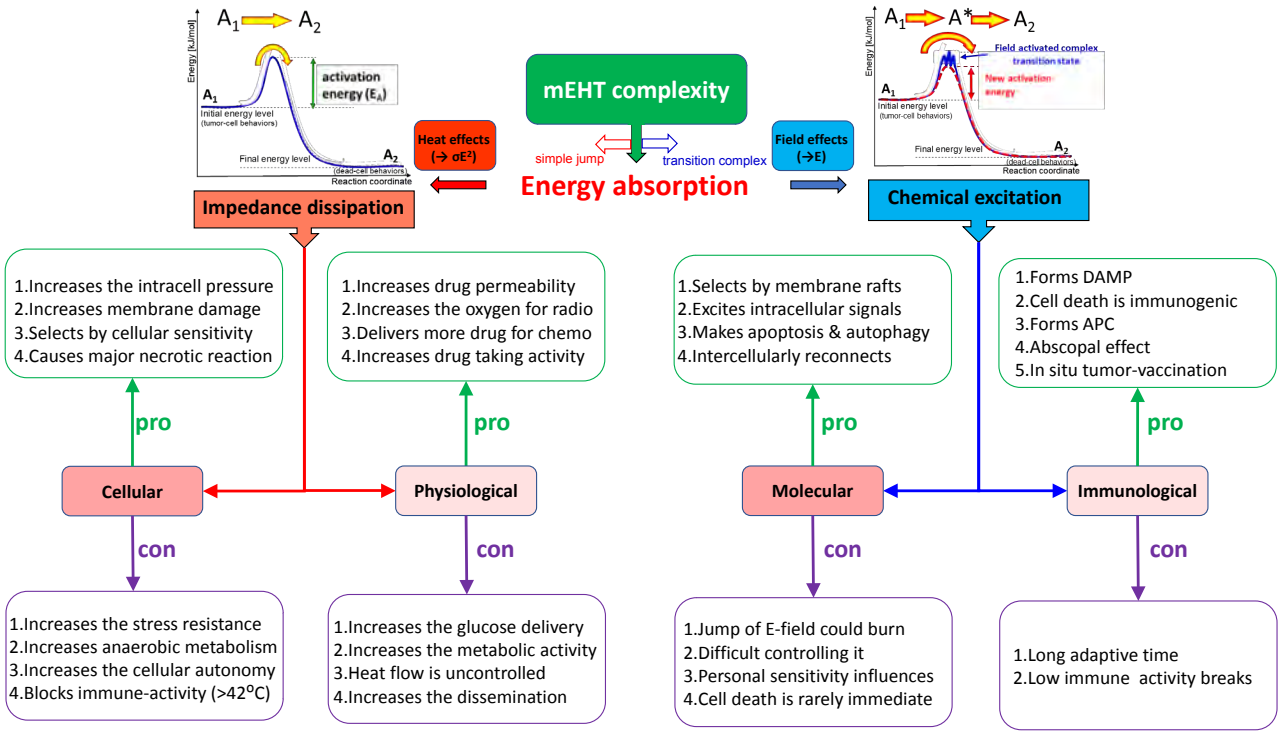


Figure 15. The complex system of the mEHT effect

electrohyperthermia (mEHT, trade name oncothermia®) specialized on the electromagnetic resonances with time-fractal modulation. The mEHT is a kind of specialized hyperthermia, where the electric field has a double role. The thermal energy dissipation is proportional to the electric field's square, while the molecular actions depend on the field linearly. The two parts of the complex impedance are equally applied in this method, **Figure 15** [203]:

1) The square (the absolute value) of the field is responsible for the heating. This process depends on the conductivity of the target.

2) The field vector makes the excitation, working resonantly like an enzymatic action, lowers the energy barrier (the activation energy) through a transition state. This process depends mostly on the dielectric properties of the target.

The modulated electro-hyperthermia (mEHT) applies to these researches in preclinical experiments [197] and clinical applications [198].

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Conflicts of Interest

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

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Dosimetric Evaluation of the Scanning Activity at the Regional Hospital of Kaolack (Senegal)

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Abstract

The aim of this study was to evaluate the dose delivered to patients during scannographic examinations at the Kaolack Regional Hospital (one of the 14 regions of Senegal located in the center-west of the country, 192 km from Dakar) and to compare these irradiation doses at diagnostic reference levels found in the literature in order to optimize our scanning protocols. To achieve this goal, we carried out a prospective study involving 218 CT scans. These examinations focused on cerebral, thoracic, abdominopelvic and lumbar spine acquisitions made in adults and cerebral only in children. We compared the median values of dosimetric indicators (CTDIvol and DLP) per acquisition with NRDs in the literature. During the course of this study, we found a dosimetric ratio lower than that of the NRDs for thoracic, abdomino-pelvic and lumbar spine CT scans in adults and a significant dosimetric exceedance for brain scans in adults and in children. These results encourage us to extend these dosimetric evaluations to other hospital structures in order to establish rigorous monitoring of dosimetric indicators and to respect the principles of radiation protection and good practice.

Keywords

Dosimetry, CT, DRL, Senegal

1. Introduction

Computed tomography is based on the fact that different tissues in the body

achieve differential X-ray attenuation. The relatively homogeneous beam at the entrance becomes inhomogeneous. This information, called a radiant image, forms a real image with an appropriate sensor. These are obtained at the cost of a certain irradiation of the patient which leads to more or less long-term biological effects. This is why it seems judicious to respect the contraindications, and all reasonable technical means must be implemented to reduce these irradiation doses as much as possible while maintaining the good contrast of the image [1]. Nowadays, there is an increased demand for sometimes unjustified CT scans. This leads to deleterious effects, the most frequently encountered in medicine being the stochastic effects. We could not establish thresholds as these effects are at low doses and are also random [2]. These repeated doses, compatible with cell survival, are at the origin of DNA alterations resulting in carcinogenesis for somatic cells and transmissible genetic alterations for germ cells [3]. Two studies were carried out in Senegal concerning DRLs. One was carried out at the CHNU of FANN by DIOP [4] and collaborators and focused on conventional radiology. The other study concerned the X-ray scanner, and was carried out at CHN Aristide in Le Dantec by El Madrouchi and collaborator [5]. These two studies required supplementation with a choice of appropriate parameters to answer the question of radiation protection of patients with reference levels requiring optimization [6].

It is for this purpose that the International Atomic Energy Agency as well as other similar organizations in the world such as EURATOM, have laid down the general principles of the protection of patients exposed to ionizing radiation during an act for diagnosis purposes. In addition to explaining the steps necessary for the radiation protection of patients, it recommends, to member states, the development and use of diagnostic reference levels (DRLs) for radio-diagnosis examinations in particular CT scan [7].

The aim of our work was to compare the irradiation doses delivered to our patients with computed tomography NRD values found in the literature in order to make corrections to our protocols when necessary.

2. Materials and Methods

2.1. Material

This was a prospective, descriptive and analytical study carried out over a period of 3 months from February 17 to May 17, 2020. The data collection was done at the medical imaging department of the EL HADJ IBRAHIMA NIASS regional hospital of Kaolack, city situated in the central west of Senegal. During the study period, we received 288 patients for CT examinations and have adopted the criteria set by decision n˚ 2019-DC-0667 of the Nuclear Safety Authority (ASN) of April 18, 2019 relating to the methods for evaluating the doses of ionizing radiation delivered to patients during an act of radiology [8]. After applying the inclusion criteria, five types of scanners were studied, depending on the body area explored and the age category.

For the adult population, we performed 102 brain CT scans, 31 thoracic CT scans, 43 abdomino-pelvic and 32 lumbar spine CT scans.

For the pediatric population, we performed 10 brain CT scans in a population of children from 5 to 10 years old with a weight between 20 and 30 kg.

2.2. Methodology

The examinations were carried out on a multi-slice helical scanner from SIEMENS model 2010 (Muenchen, Germany), equipped with 16 strips.

The scanner incorporates an irradiation dose reduction technique (CARE Dose-4D) and the load can thus vary from 30 to 500 mA.

The CT presented in post-acquisition a dosimetric report on which appeared the doses delivered expressed in CTDI vol and in DLP for each acquisition and for the entire examination, as well as the length explored. The parameters that allowed the study to be carried out were voltage (kV), load (mA), acquisition thickness, rotation speed, collimation (mm) and expected length. These examinations were carried out according to predefined standard protocols. The voltage was set at 130 kV for adults and 110 kV for children. The load adopted was 220 mA for brain acquisition and other types of acquisitions with automatic milliamperage modulation. This could be lengthened or shortened on the topogram, compared to the length provided for in the protocol.

As for the dosimetric parameters, we studied the volumetric CT dose index (CTDI vol.). The length explored was modifiable as was the dose length product (DLP). Statistical analysis of these data was performed by dedicated statistical analysis software SPSS, version 18 and graphical representations made by Microsoft Excel 365 software

3. Results

3.1. Dosimetric Evaluation in Adults

3.1.1. Brain CT

The value of the flight CTDI was constant at 58.3 mGy. The median value of the lengths explored was 188.5 mm with extremes ranging from 159.5 mm to 341.5 mm with a ratio. The 75th percentile and the 25th percentile are estimated at 211.25 mm and 177 mm respectively, *i.e.* a 75th/25th percentile ratio estimated at 1.19. For DLP (**Figure 1**), the median was 1098.94 mGy·cm, with a standard deviation of 270.95 mGy·cm with extremes ranging from 929.87 to 1990.92 mGy·cm. The 75th/25th percentiles were estimated at 1257.07 and 1031.91 mGy·cm respectively, *i.e.* a 75th/25th percentile ratio of 1.21.

3.1.2. Thoracic CT

The median value of the flight CTDIs was 6.13 mGy with a standard deviation of 2.55 mGy and extremes of 2.85 and 14.4 mGy. The 75th/25th percentiles are respectively estimated at 8.22 and 5.19 mGy, *i.e.* a 75th/25th percentile ratio corresponding to 1.58. As for the median value of the lengths explored; it was estimated at 356.4 mm with a standard deviation of 97.4 mm and extreme values of

Figure 1. Distribution of PDL values for brain CT scan in adults.

269.4 and 734.7 mm. The 75th/25th percentiles are estimated at 384.7 and 330.9 respectively, *i.e.* a 75th/25th percentile ratio of 1.16.

For DLP (**Figure 2**), the median was 218.58 mGy·cm, with a standard deviation of 96.1 mGy·cm and extremes of 91.95 and 444.1 mGy·cm. The 75th/25th percentiles were estimated at 355.43 mGy·cm and 188.29 mGy·cm respectively, *i.e.* a 75th/25th percentile ratio of 1.88.

3.1.3. Abdomino-Pelvic Scanner

The median value of the flight CTDIs was 5.61 mGy with a standard deviation of 1.3 mGy and extremes of 4.26 and 9.65 mGy. The 75th and 25th percentiles are respectively estimated at 6.78 and 4.26 mGy, *i.e.* a 75th/25th percentile ratio corresponding to 1.3. As for the median value of the lengths explored; it was estimated at 498.7 mm with a standard deviation of 44.84 mm and extreme values of 438.2 and 679.2. The 75th/25th percentiles are estimated at 520.7 and 470.7 mm respectively, *i.e.* a 75th/25th percentile ratio of 1.1.

For the DLP (**Figure 3**), the median was 281.91 mGy·cm, with a standard deviation of 71.45 mGy·cm and extremes ranging from 200.27 to 503.38 mGy·cm. The 75th/25th percentiles were estimated at 333.3 mGy·cm and 241.74 mGy·cm respectively, *i.e.* a 75th/25th percentile ratio of 1.37.

3.1.4. CT Scan of the Lumbar Spine

The median value of the flight CTDIs was 10.39 mGy with a standard deviation of 3.45 mGy and extremes ranging from 5.05 to 21.09 mGy. The 75th/25th percentiles are respectively estimated at 11.82 and 8.91 mGy, *i.e.* a 75th/25th percentile ratio corresponding to 1.32. As for the median value of the lengths explored; it was estimated at 285.45 mm with a standard deviation of 112.79 mm and extreme values varying from 230.2 to 616 mm. The 75th and 25th percentiles are estimated at 327.82 and 268.3mm respectively, *i.e.* a 75th/25th percentile ratio of 1.22.

For DLP (**Figure 4**), the median was 310.55 mGy·cm, with a standard deviation of 159.12 mGy·cm and extremes ranging from 169.04 to 876.43 mGy·cm. The 75th/25th percentiles were estimated at 426.32 mGy·cm and 245.09 mGy·cm respectively, *i.e.* a 75th/25th percentile ratio of 1.73.

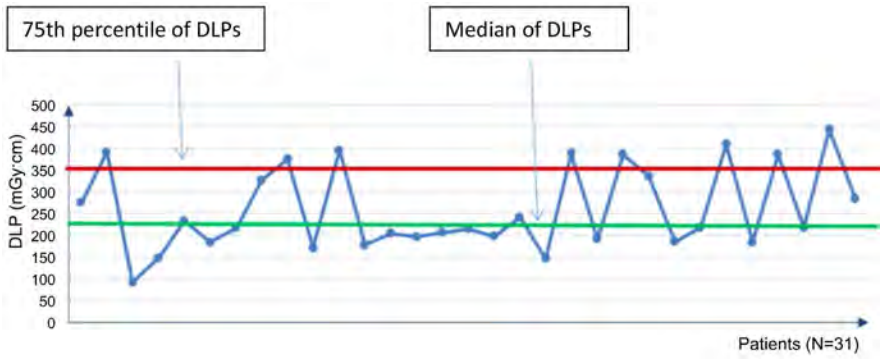

Figure 2. Distribution of DLP for chest CT scan in adults.

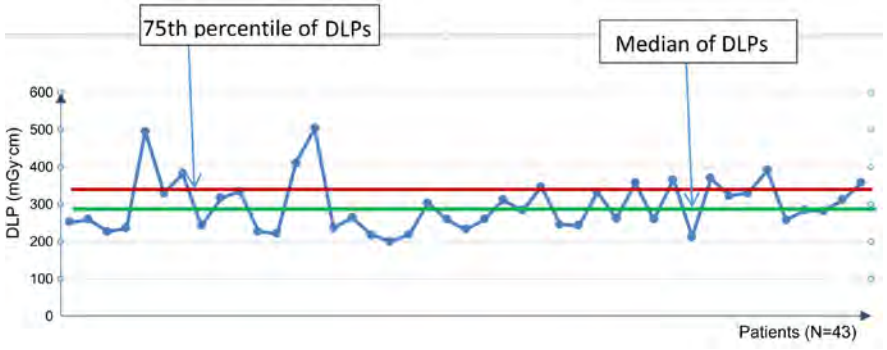

Figure 3. Distribution of DLP for abdominopelvic CT scan in adults.

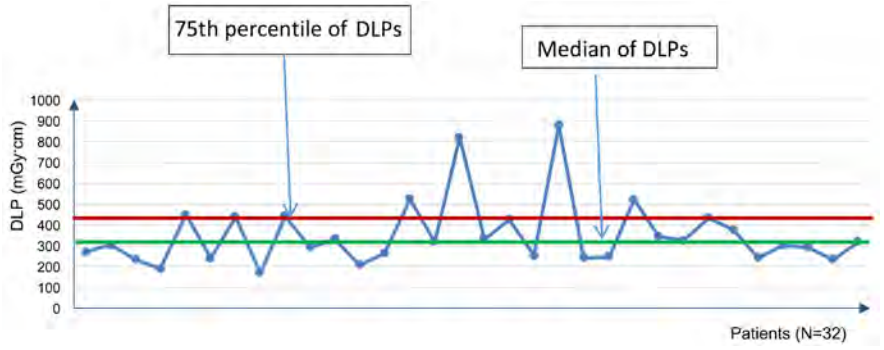

Figure 4. Distribution of PDL for CT scan of the lumbar spine in adults.

3.2. Dosimetric Evaluation of the Brain Scan in Children

The distribution of CTDI-vol values by brain scan acquisition had a median value of 25.93 mGy with a standard deviation of 3.31 mGy and extreme values of 22.94 and 31.52 mGy. The values of the 75th/25th percentiles were respectively estimated at 29.32 and 23.73 mGy, *i.e.* a 75th/25th percentile ratio corresponding to 1.23.

As for the median value of the lengths explored; it was estimated at 290.1 mm with a standard deviation of 41.38 mm and extreme values varying from 199.6 to 316.1 mm. The 75th/25th percentiles are estimated at 304.72 and 262.97 mm respectively, *i.e.* a 75th/25th percentile ratio of 1.15.

For DLP (**Figure 5**), the median was 743.57 mGy·cm, with a standard deviation

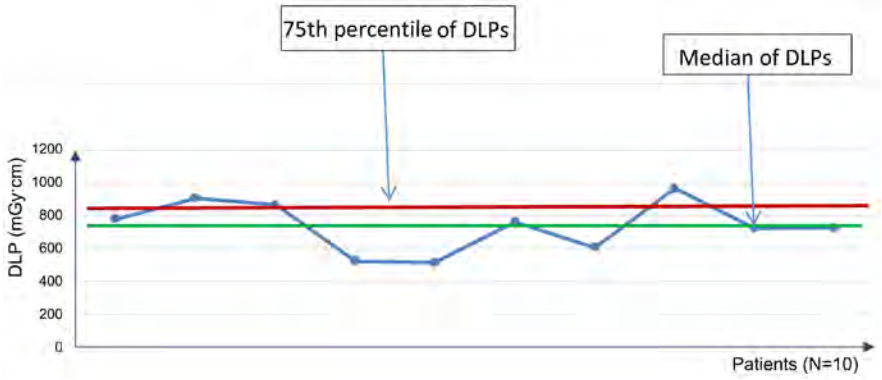

Figure 5. Distribution of DLPs for the brain scan in children.

of 153.87 mGy·cm and extremes ranging from 513.63 to 964.76 mGy·cm. The 75th/25th percentiles were estimated at 843.41 mGy·cm and 633.89 mGy·cm respectively, *i.e.* a 75th/25th percentile ratio of 1.33.

4. Discussion

4.1. Dosimetric Evaluation in Adults

4.1.1. Brain Scanner

The value of the flight CTDI was constant at 58.3 mGy, higher than the NRD value in the USA [9] which is 56 mGy, that in Belgium [10] which is 50 mGy and that in France [8] which is 46 mGy. The median value of DLP was 1098.94 mGy·cm, higher than the NRD value in the USA [9] which is 962 mGy·cm, that in Belgium [10] 800 mGy·cm and that in France [8] 850 mGy·cm.

As in our study and with this type of brain examination carried out in adults, the only parameter modifiable by the manipulator technician was the length explored and, moreover, the irradiation dose reduction software (CARE Dose-4D) did not work, this could explain the superiority of our values of CTDI and DLP compared to those found in the literature. We also observed that the median value of the lengths explored was 188.5 mm and is much greater than the length provided for by the predefined protocol (150 mm), with an inclusion in the field of exploration of anatomical areas not interested in the desired study, hence the need for compliance for this type of examination. For this, it seems judicious to us to limit ourselves to the irradiation field, to the anatomical zone useful for the study and also to study the possibility of integrating the dose reduction software for this type of examination.

4.1.2. Thoracic, Abdominopelvic and Lumbar Spine Scans

The median values of CTDIvol were lower than the values of NRDs in the USA, Belgium and France.

The median values of the lengths explored were relatively high compared to the length provided for by the protocol, especially for scans of the lumbar spine where several of our examinations went back to the dorsal vertebral level or covered the entire pelvis.

We insisted with the manipulator technicians on the importance of respecting the acquisition lengths. The normal height of acquisition for the lumbar spine should extend from the twelfth dorsal vertebra to the sacroiliac joints.

The median DLP values were lower than the NRD values in the USA, Belgium and France.

Although the lengths explored are relatively high, the use of the irradiation dose reduction software (CARE Dose-4D), allowing the automatic modulation of the load according to the different regions crossed by the X-ray beam, means that the median values of the vol and DLP CTDIs remain lower than the NRD values [11].

4.2. Dosimetric Evaluation of the Brain Scan in Children

The median value of CTDIvol was 25.93 mGy, lower than the value of NRD in Canada [12] which is 51.5 mGy, that in Belgium [8] which is 40 mGy and also that in France [8] which is 26 mGy.

The median value of the lengths explored was 290.1 mm, much too high compared to the length provided for by the protocol (150 mm).

The median value of DLP was 843.41 mGy·cm, higher than the value of NRD in Canada [12] which is 692 mGy·cm, that in Belgium [10] which is 660 mGy·cm and also that in France [8] which is 470 mGy·cm.

Despite the use of radiation dose reduction software (CARE Dose-4D) for this type of scanner, the DLP was significantly higher than the NRD values. This can be explained by a lack of training of our technicians, whether for acquisition techniques, with inclusion in the field of exploration of anatomical areas not interested in the desired study, or radiation protection rules for the patient.

5. Conclusions

The improvement of the scanning practice requires, first of all, a good knowledge of the fundamental principles of radiation protection applied to the medical field: the justification of the clinical indication and the choice of the radiological examination, optimization by informed management acquisition parameters to achieve the compromise between lower dose of irradiation and better image quality, known by the acronym "ALARA" (As Low As Reasonably Achievable) and finally substitution when the limitation is not beneficial to the patient.

In Senegal, it would be useful to introduce legislation that requires an assessment of the radiation doses delivered to patients during diagnosis and interventional radiological examinations against national reference values. These evaluations would be periodic and monitored and corrective actions would be imposed as needed.

The transposition of the dosimetric record in our reports should be compulsory. Relevant information is DLP for any exposure and CTDIvol for pelvic exposures in women of childbearing age and in pregnant women after justified

exposure.

The initial and continuing training in radiation protection of the various stakeholders must be an ethical or even legal obligation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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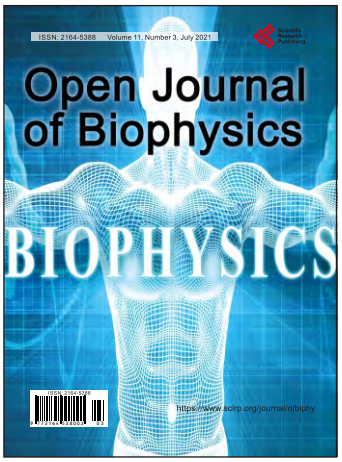

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