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Electromagnetic effects in nanoscale range*

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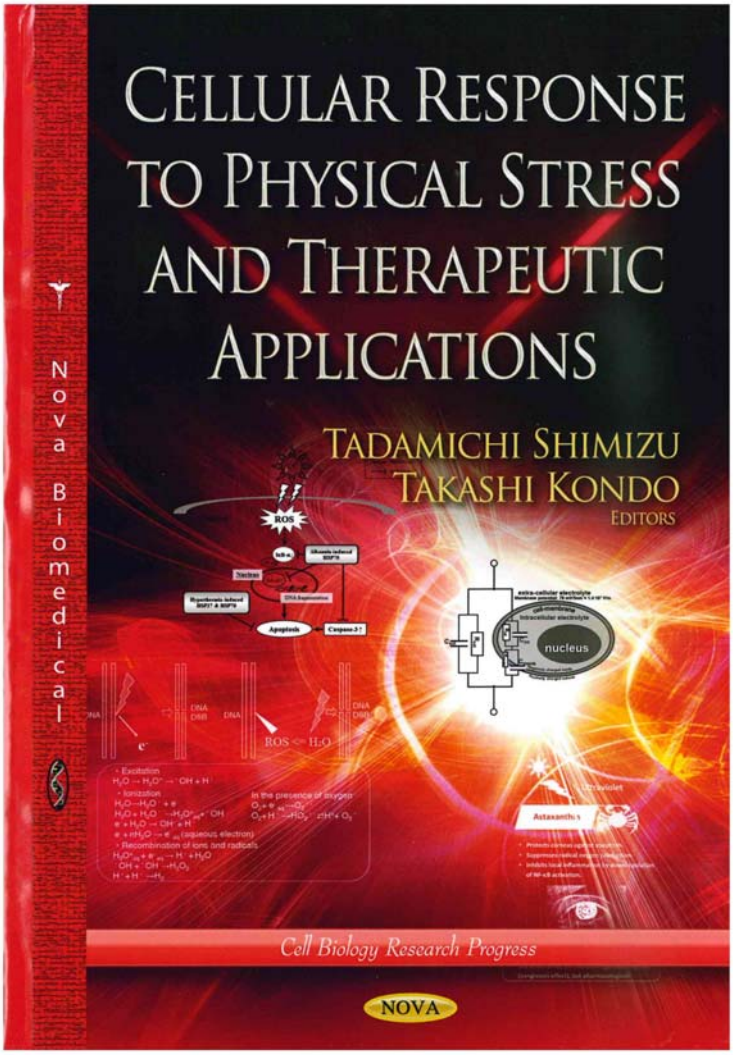

Abstract

Hyperthermia method was "reborn" with the electromagnetic applications a century ago when deep heating became a realistic goal. The lack of its wide application is that the locally targeted volume has physiological consequences; the systemic control of the human body tries to compensate the active deviation from the homeostatic equilibrium. Clues for the success of the proper hyperthermia treatment are: (1) accurately select the tumor; (2) do not excite the homeostatic correction feedbacks (like blood-flow); (3) properly select the malignant cells; (4) use an effective cell-killing method for the malignant cells; (4) act on innate and adaptive immune system completing the job. Our objective is making the selected concentration of the electromagnetic energy on the sensitive points of the malignant cells, providing energy liberation in this cellular nanoscopic region by nanothermia (modulated electrothermia).

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1. Challenges of local hyperthermia

Heating as medical application has outstanding history from the ancient medicine to the currently used therapies. There are numerous medical advantages of the local heating, which are applied in oncology too. However, doubts are fueling intensive debates about the possibilities of clinical hyperthermia [1].The main question, is open: "What is against the acceptance of hyperthermia?" [2].

The real challenges are the controversial results. This happened in a cervical cancer study where the results were very promising [3], and a control study [4] was disappointing.
What is the origin of these problems? Naturally, it is the complex physiological reaction of the human body to the local heating actions.

The locally or systemically increased blood-flow tries to compensate the growing temperature and cools down the target volume. The provided heat energy (the specific absorption rate SAR), irrespective of how accurately it was focused, will be drastically modified by the blood-flow. In consequence, the SAR pattern and the temperature mapping of the targeted volume are significantly different [5]. The reference point is definitely missing which explains the contradictory results [6].
The human body actively tries to down-regulate the enhanced temperature, by complex homeostatic control.

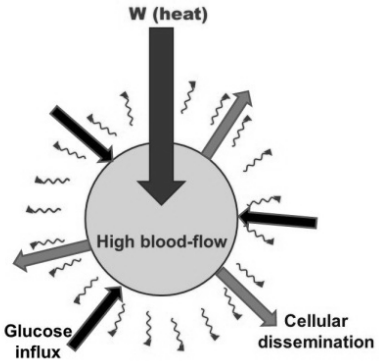


Figure 1. The temperature naturally spreads and increases the blood-flow. A competition starts: the cell destruction potential is higher or the tumor-energizing by glucose supply combined with higher risk of the metastatic potential will win.

The temperature regulation intensifies the blood-flow to keep the body isothermal. Together with the larger incident energy, the activated blood-flow has further, definitely negative effects (see Fig. 1.):

- delivers more nutrients (glucose) for tumor survival
- increases the risk of dissemination of the malignant cells.

These both support the malignant process, drastically limiting the prognostic chances of the patient. Anyway the only local action is not enough, the cancer is a problem of the tissue-organization [7], and cannot be regarded as an isolated tumor in the body.
With the application of local heating, the competition starts between the cell-killing potential of the heat and the cancer-supporting potential of the gained blood-supply by higher temperature of the targeted volume. There are special bio-currents exist: the injury currents [8].The electric field

in the tissue is oriented in the wound area, and the current has a closed loop through the surface of the epithelium, with the current from inside to the surface of the wound itself. It regulates the orientation and the frequency of cell-division [9], directs the cell migration to heal [10]. The injury current also has a positive feedback loop by the homeostatic control. The growing tumor enlarges the disorder and creates different dielectric proprieties of the tumor volume from its healthy environment. This induces injury current, which grows with the development of the disorder, and tries to repair the "wound" [11].

Whereas conventional oncologists don't use, or even tell their patient not to take, the antioxidants because they could interfere with the oxidative action of chemo-drugs, integrative oncologists, like us, use a number of antioxidants. Conventional therapy sees the need for the chemo agents to act for several days to damage as many dividing cells as possible. Our integrative therapy concept does not need this because with IPT and hyperthermia we target the cancer cells when the drugs are administered and kill them together with hyperthermia.

2. Deep-heating for local-regional hyperthermia by electromagnetic effects

There are various local-regional hyperthermia devices working on electromagnetic principles. All the main categories of the electromagnetic interactions (e.g. magnetic, electric, radiative, galvanic) are used in various technical realizations, [12].

The magnetic field application has the weakest coupling, to strengthen it sometimes magnetic materials are inserted in the target (nano-particles, rods, seeds, etc.) [**12**]. The antenna coupling is stronger, more energy could be absorbed by the target. To increase the deep energy delivery and the focusing on the target, usually an antenna-array is applied around the target. Their energy absorption ability is increasing in the subsequent order as: magnetic, radiative, capacitive, galvanic. (Historically the development had the opposite direction from the strong to the weak coupled methods.) When the coupling is weak, the control of the absorbed energy needs extra information, while in case of strong coupling, the electric circuit parameters are usually enough to control the absorption of energy by the target.

Due to the certain gradient of the dielectric constant at the membrane, the outside electric field modifies the polarization, the induced charge density distributes non-homogeneously on the cellular surface. This charge remains stable only for a short time ([13]), but its amount depends on only the conductivity of the media and the interstitial electric field. The gradients in one single half-period are in contrast with the situation in the next half-period. When the field changes its direction, consequently the charges are also formed oppositely, so a vibrating dipole is created with the frequency of the outside field. The RF-current has a positive phase shift, due to the complex value of the conductivity of the matter, which also makes a frequency dependent (dispersion) connection between the field and the induced charge. The inhomogeneity of the complex value of the conductivity has less influence on the value of the space-charge than the permittivity does, because its changes are logarithmically "dumped".

There are considerations that the malignant tissue has a certain potential gradient to its healthy neighborhood [14], which acts to promote and direct the cancer-cell migration. There are increasing number of arguments on the cancerous process as a wound repair [15]. The bio-system falsely recognizes the tumor as a wound, and stimulates its environment to heal the irregularity (meaning to produce cells to heal). This wound-healing mechanism is actively supported by the actual injury currents due to the potential gradients.

Historically, the technical development started with strong coupling solutions and had a gradual progress in the directions of weaker couplings.

In fact, most of the strongly coupled conductive (resistance) heating was the very first "modern" method of oncological hyperthermia, started in the late 19th century, and was called "galvanocautery" , and more recently the "biologically closed electric circuits" (BCEC) [**14**], was developed and were found effective against some tumors. The methods were further developed in two temperature oriented, definitely invasive branches: the interstitial hyperthermia [16], and the ablation techniques [17].

The first capacitive coupled device was launched in the1920s. There was a great restart of this method in 1976 [18] and it has been widely applied ever since, [19]. Most hyperthermia devices use capacitive coupling due to their relatively easy technique. Its efficacy was discussed and proven in the relevant literature, [20]. The typical frequency for capacitive coupling is in the range of 5-30 MHz. However, it was becoming more and more clear, that the knowledge of the radiofrequency technique alone is not enough for the successful development, the refining of the system for the physiological effects is the clue of the success, [21].

The radiative microwave techniques gave a new support for hyperthermia.The generations of the antenna-array coupling, the annular phase array [22], and the matched phase array [23] were developed.

Treatments with coils (magnetic and inductive) are relatively rarely used due to the negligible magnetic permeability of the living systems. In order to improve the magnetic energy absorption, microparticles, ferrite rods, are usually injected into the targeted area. Using the same idea, a new "intracellular hyperthermia" method was developed, however, the efficacy of this treatment is still debated. Emerging application of magnetic treatments started by the nano-particle magnetic suspensions. Other inductive heating uses only induction of Eddy-currents,, without inclusion of the extra magnetic material. This method has low efficacy, but its penetration is definitely large.

The electric-engineering generally considers linear effects of the electromagnetic fields in the targeted material; supposing the electric and magnetic polarization proportional with the outside fields. It is mostly correct in the non-living homogeneous solid states, but incorrect for living objects. All the living materials contain definite highly polarized layers (membranes) which are not proportional at all with the outside fields. Furthermore, there are mixture of various components of the living matter having different frequency dispersion. The frequency dependence of the electric impedance of the bio-matter varies their energy-intake too. The conducting electrolytes in bio-matter are all "encapsulated" by various membranes and wall-structures (see Fig. 2.).

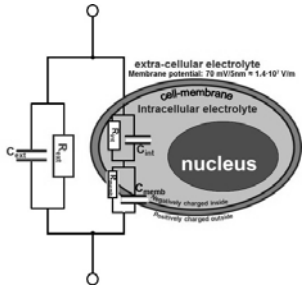


Figure 2. Electric schematics of one electrolyte "capsule", namely the cell.

Most of the "encapsulating" materials are good electric isolators, forming capacitance. Hence, the average bio-impedance behaves like a (non- perfect) capacitor. This complex structure makes the phenomena highly non-homogeny and complicated, their impedance is described by semi-empiric formula [**13**]. The currents flow through the system could force a sliding energy-bag (bio-solitons), [24]. The various tissues represent different overall impedances, giving possibility to distinguish them by electric measurements. The method has been approved for a long time by the FDA for breast diagnostics.

Despite the microscopic details are far from linearity, but for studies we are using great averages and some empirical rules the bio-matter could be handled in the frame of linear electromagnetics. In this point of view, the material is characterized by its dielectric properties. Generally we use complex number for dielectric constant (ε*). The real part of it is the permittivity (ε'), while the imaginary one (ε'') is proportional with the conductivity (σ) and inversely proportional with the actual frequency and all of these have dispersions in frequency. The absorbed energy in a unit volume in Debay relaxation approach is proportional with the conductivity and square of the electric field, while a part of the energy oscillates in-and-out by double frequency, having no real heating, proportional with the permittivity.

The data has to be modified by an experimental fact, showing the membrane capacity is also frequency dependent by an exponent α. Its value could be used to distinguish between the healthy and malignant situations [25]. Studying the differences between the malignant and healthy tissues, the exponents deviate: αmalignant=0.56 αhealthy=0.47, [**25**]; and the characteristic frequency of the function of imaginary part of impedance Z, is measured as significantly different, the measured index (IR) is typically: IRmalignant=1.8, IRhealthy=0.68.

There are questions about the penetration depth of various electromagnetic effects into the body to target deep-seating volumes. The interaction takes energy from the incident action. The penetration is naturally infinite when no interaction, so the target is completely transparent. The penetration depth has a meaning, when the interaction is non-zero and so the energy loss determines the effect layer by layer, steadily reaching a depth, when the actual interaction is not available evermore due to the too low energy to excite it. Usually the electric field has exponential decay by depth, having a long "tail" until shrinking below the excitation threshold. Simply, the penetration is defined by the depth when the incident electric field loses its ~63%, so drops to ~37% of its initial value, (see Fig. 3/a.). This however, does not mean that no deeper penetration exists, the loss remains the same percentage in two, three etc. times deeper distances: ~13.7%, ~5%, ~1.9%, ~0.7% of the incident energy. The penetration depth (d) can be calculated [26]. The 10 MHz region of the excitation has ~20 cm penetration in average human tissue, while this value is drastically lowered by increasing frequency. In microwave range, the penetration goes below 1 cm. The penetration of the field and the penetration of the energy delivered by it is different, due to the fact that the energy is proportional with the square of the fields, so the depth, when the energy decreases by 63%, is shallower. On the other hand, when the magnetic component makes the effect (like in case of NMR), the penetration is deeper. The field penetration depth does not mean that all the effects follow the same rule. The penetration is only an orienting parameter, not decisional at all.

The important factors for the depth are the thresholds of the interactions, which are actually studied. The real penetration of the studied action is different, it is determined by the actual interactions (see Fig. 3/b.). There is of course action possibility of the less than 5% of the incident beam, which is three times more than the definitive "penetration". The "depth of action" is tightly connected to the dose too. The interval depends on the time duration of the action, and could be modified well (shifted or elongated) by the treatment time.

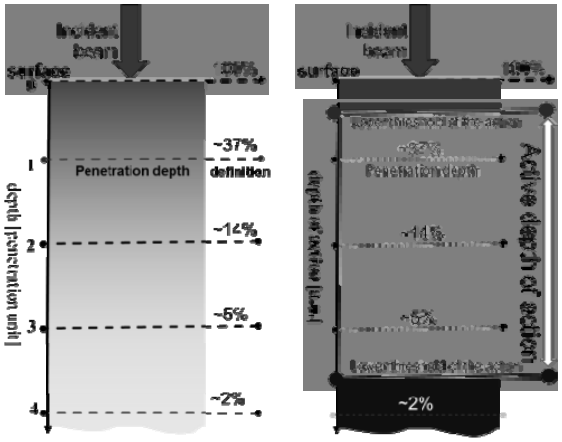


Figure 3. The penetration depth is the distance where the initial beam energy (or field) decreases by ~63% (a). The real penetration from the point of view of the studied action is different (b).

Generally, we know the interval when the reaction can happen; there are upper and lower thresholds to find the action valid. These thresholds define the penetration for the actual interaction. For example, when the important factor is the cellular apoptosis, probably the high energy layer on the top is excluded, because of the necrosis, and also there will be a depth, when the effect which causes the apoptosis cannot be generated due to the weak signals. The real depth of the apoptosis is an interval and not a threshold. A clear example for the difference of the definitive penetration depth (DPD) and the depth of action (DA) is the study of the ruby laser to the skin, [27]: when DPD was ~1mm, the DA was measured as 14.8mm, ~14 times longer! The 2400 MHz microwave-oven radiation has less than 1 cm penetration depth, but of course it does not mean you are not able to heat-up deeper. In the study of "thermal and non-thermal effects" the penetration depth is also orienting only, [28].

The upper threshold of the "penetrating action interval" is usually modified with safety parameters too. The power density of the targeted surface has a safety limit [29]; not more than 0.5 W/cm^2 incident beam can be applied when intending to use the effect for 60 min.

3. How local is the "local"?

The question arises: how locally do we have to heat? Do heat up the entire body to increase the complex immune actions [30], or heat up the complete region where the tumor is [**13**], or heating only the malignant tumor locally [31], or localize the heating only to the nanoparticles in the targeted volume [32]. These various targets (ranging more than nine (one billion) order of magnitudes in size) surely need different mechanisms and different techniques to use, despite the same tumor is treated.
A few millimeter diameter is the smallest spot to heat inside the body by artificial focusing. This focus needs sophisticated techniques, and there are a few millions of cells in, together with various liquids and components. Nevertheless the accurate locality, the pumped heat spreads by the time and equally heats up the entire neighborhood, the complete volume more extensive than the size of the spot.

However, when only a very small mass (a cell) is selected and heated up to high temperature, the situation is very different. The mass of a cell is ~100 million times smaller than the smallest artificially focused target is, so its temperature spreading is negligible in its wide neighborhood, because its energy-content is too small even when it has extremely high (over 50°C) temperature. When the malignant cells could be selected individually, the overall temperature would be negligible despite the extreme high local cellular temperature. However, when the overall

transmitted energy is too high we obtain the classical doubtful situation, the physiological feedbacks work against our efforts, (see Fig. 4.).

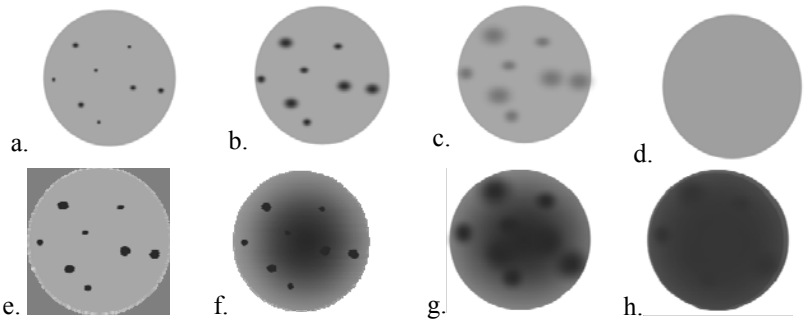


Figure 4. Spreading of the heat at nano-scale heating (oncothermia), where the power is small but it causes selectively high temperature in nano-range, the overall temperature increase is negligible (a→d);while in case of high power absorption the unselective macro heating situation is realized (e→h), which tends to isothermic, the selection by thermal gradients disappears. [(a→d & e→h show the situation by the elapsed time.]

Heating up only the malignant cells to high temperature, we have to select them with high preciosity. While the conventional hyperthermia focuses and targets a macro region, the nanoheating (oncothermia) process, acts in nanoscopic range without any extra selectors (added nanoparticles), selecting the membrane of the malignant cells directly. It is similar to the nanoscopic action of the ionizing radiation, which acts on selected nanoscopic point in the cell, destroys the DNA strands. The nanotherapy (oncothermia) selects the cell-membrane of the malignant cell or at least induces apoptotic cell death from there.

4. What does „non-thermal“ mean?

The category “non-thermal” is widely used in the professional [**28**], [33] and popular (‘electrosmog’) literature, [34].

The “thermal effect” is misused in the hyperthermia literature making equivalent with the “temperature dependent” effects. The most obvious action of the electromagnetic energy absorption to living objects is the temperature increase indeed. However, in most of the cases the category “thermal” means chemical (changing the chemical processes) or structural (rearranging the structures) effects in the living matter. In thermodynamical point of view however, all the changes, which modify the internal energy of the system are thermodynamical (“thermal”) irrespective of the changes of the temperature.

To show the difference, let us study the well-known phase transitions of water. Ice, when melted, has to be heated up producing liquid water, and the temperature of the mixture does not change while the ice is melted. We have the same experience during cooking, its temperature does not change until the full liquid is transformed to gas (vapor). These processes happen at definite, stable temperature in ambient pressure, but the temperature does not change until the process is completed. It would not be correct to say that these processes are non-thermal. These are thermal, but not temperature dependent (NTD); while the temperature remains constant. The electrochemical reactions [35] are also NTD. The process, during the phase transition, cannot be characterized by temperature in the cells [36]. The energy, which is pumped in, is expended to break the internal bonds (make phase transition), and not to rise the temperature until the process is over.

All living systems have controlled energy-combustion. Their metabolic activity has a scaling behavior by the mass of the organism in all the ranges of the living matter from the subcellular to

the complete system, [37]. NTD effects are usually referred to in the interactions with the electromagnetic fields, having not enough energy to increase the temperature, but the effect of the applied radiation (field) is measurable.

Targeting chemical bonds is a nano-scale effect. The temperature dependent effects, however, are definitely macro-scale processes. The electromagnetic interactions are definitely nano-effects, interacting with the various charged particles and their dipoles and significantly act on their dynamic properties (transports, collective movements, etc.) too.

Spectacular experiment was presented, when the same temperature is reached by conventional and microwave heating, and the reaction was significantly different [38]. A large series was published about the NTD electric field mechanisms on DNA transfection, [39]. Effect of electromagnetic fields on DNA was studied as a charge distribution effect, [40], and tried to explain the molecular mechanism of ion-pumps influenced by outside electric fields, [41], which later had a controversial debate, [42].

The electromagnetic field directly affects the large, complex molecules like proteins and DNA, [40]. It was shown much earlier [43], that the exposed charge of the protein remains constant on the area effectively exposed by water, irrespective of the size. This leads to the conclusion, that the extra area enlarging the water-exposed surface by unit charge is proportional with the inverse of the charge density [40].

The AC-field induced ponderomotoric forces (typical NTD), was studied by Schwan [44] as early as in 1982 and the redistribution of the membrane receptors is also possible by action of AC [45]. Numerous applications of alternating current (AC) are effectively applied for cancer treatments, [46]. There are various applications of the alternating field from the power-line frequencies (50-60 HZ) [47], supplied by theoretical considerations [48].
The accurate selection of malignant cells is a key step of the proper hyperthermia. For proper selection, there are the robust electromagnetic differences between the malignant and healthy cells, which are used by modulated electrothermia. These (see Fig. 5.) are:

1. Differences of metabolic rate of the malignant and healthy cells (Warburg effect, [49]);
2. Differences of the dielectric constant of the extracellular electrolyte and membrane-bound water of the malignant and healthy cells (Szent-Gyorgyi effect, [50]); accompanied by the δ-dispersion process (Schwan effect [51]).
3. Structural differences (pathological pattern recognizing) of the malignant and healthy tissues (fractal physiology effect, [52]).

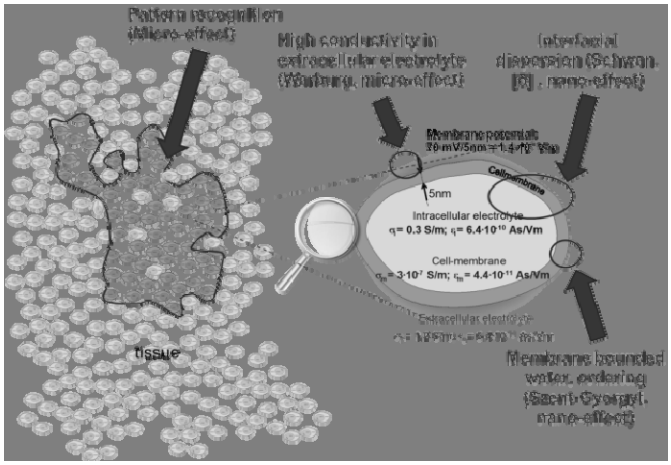


Figure 5. Main selection factors of the modulated electro-thermia (nano-thermia, oncothermia) method.

5. Selection by metabolic rate of cells

Otto Warburg discovered the definite metabolic deviation of malignant cells, originated from mitochondrial dysfunction, [53]. According to Warburg's main idea, the primary cause of cancer is the glycolysis. Malignant cells use fermentation in utilizing the glucose to produce 2ATPs, while the normal Krebs cycle uses the oxidative way, producing 36ATP with high efficacy, [54]. Despite the fact that the fermentative way produces 18-times less ATP, the simplicity of the process favors this way, similarly to the well-known change of glucose metabolism in the sport-medicine to supply the ATP demand by muscle activity.

The high glucose influx, which is necessary for the energy supply of malignancy, creates distinguishable difference in composition of the extracellular electrolyte in the vicinity of these cells. This difference is used anyway in the modern diagnostics (positron emission tomography, PET, [55]). The highly concentrated metabolites significantly increase the ionic concentration of the extracellular electrolyte. Approximated from the positron annihilation data, the glucose influx of the simple fermentative reaction could be even 100 times larger, than the regular oxidative way. The large glucose demand and the lactate production intensifies the transports.

The composition change of electrolytes clearly selects between the cells of different metabolic forms and focuses the RF-current automatically on the extracellular electrolyte of malignant cells. The irregular behavior of electric conduction can be measured and imaged by the Electric Impedance Tomography (EIT). Also, this effect could be applied in prophylactics like mammography [56] too. The increase of the current density in the tumor could be visualized by MRI (RF-CDI), [57].

6. Selection by dielectric properties of cells and components

The living state exists in a set of aqueous solutions, where the water is mostly well ordered, [58]. The order in healthy tissue is dominant while not so in malignant state, [59]. Rearranging (disordering) the electrolyte structure needs energy, similarly to melting of ice with latent heat. This drastic change (phase transition) modifies the dielectric constant and decreases the cell-cell adhesion, [60] without changing the composition of the medium itself. The order-disorder phase-transition indicates two different states of the cells: their autonomy status (called α-state) and their connected, the collective status (β-state), like denoted by A. Szent-Gyorgyi, [61].

The α-state is the basic status of life. In this state, the highest available entropy is accompanied with the lowest available free-energy. All complex living systems could easily be transformed into this basic state when they become instable. Then, by the simple physical constrains the cells try (at least partly) to realize the α-state again. The system (or a part of it) contains cells with high autonomy and proliferation-rate in α-state. The α-states are metabolizing dominantly in a fermentative way, while the cells in β-states dominantly have regular mitochondrial one. The high energy-flux makes the cells less cooperative and more primitive, while the low energy-flux makes the cells not only cooperative but also differentiated. The electromagnetic behavior of the electrolytes balances the concentration of β-and α-states in the highly developed living objects [62]. The order-disorder transition changes the dielectric constant and allows the additional selection (focusing).The higher dielectric constant of malignant cells absorbs more from the RF-energy, due to their disordered behavior. The ordered structure makes it possible to "channel" the energy-flow, while the disordered case absorbs the energy in a "friction like" manner.

Additional to the ordering effect there are various forms of frequency dependent energy-absorption mechanisms exist, [63]. The dominant mechanisms determine frequency intervals denoted by α, β,

γ and δ) [64]. The β -dispersion [65] (or known as interfacial polarization effect) is between 0.1-100 MHz, and it is characteristically determined by the membrane capacities of the cell and the intracellular organelles, bound-water to membrane etc. The bound water to the membrane has the upper frequency part of the β-dispersion, denoted by δ, [66]. Especially, all the electrolyte and membrane properties of the malignant and healthy tissues differ. The proper selection uses the dipole relaxation of the membrane bounded water.

The transmembrane potential could also be changed by outside electric field. The Schwan equation of electric field effect on the transmembrane potential [67] based on dispersion relation does not contain temperature, the field acts only [68], and modified by the correlation of fluctuations of the membrane connected to electromagnetic interactions, [69]. The bounded water gives δ-dispersion, [70]. A definite peak in Joule-heat refers on the energy-absorption in protein and protein-bound water structures as well as on the boundary-interface structures, [71]. The numerical evaluation of the model confirms the specialties of the various measured data around 10MHz well.

7. Selection by morphological differences of the tissues

Various tissues have distinguishable structures and an experienced pathologist can easily recognize the malignancy in the tissue sample by their deviation structures. The pattern-recognition from biopsies or other tissue-samples is one of the major proofs of the malignancy in oncological practice.

The tumor is very much complex in its pattern. The morphology is an important factor of the cellular organization, [72]. The cellular structure prefers special coordination arrangements [73], and could arrange a self-organized collectivity, [74]. Topological position of cells a factor is favoring the division, [75].

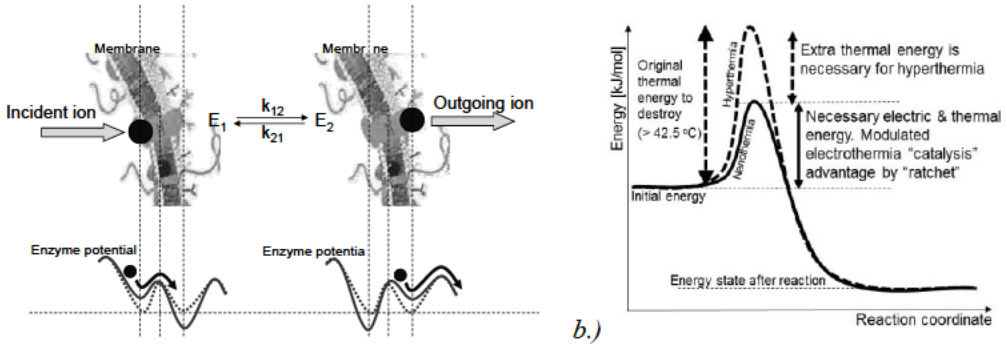
Healthy cells have special "social" signals [76] commonly regulating and controlling their life for high efficacy. The malignant transformation breaks the healthy organized transport and seeks to build up a new one for the new demands; instead of the collective signal the malignant cells are driven by individual competing cells, irrespective of the efficacy of the energy conversion.

The healthy living systems have characteristic fractal dynamism, [77], in consequence of its self-similar stochastic behavior. The healthy dynamism fluctuates by particular identified pattern, [78], having fractal behavior in space and time. The healthy time fractal is scale-independent fluctuation, ("pink noise"), which can be identified by dielectric properties too [79]. This dynamic time-fractal is the effective information exchange is the social signal between the cells, [80], [81].
The collective order is missing in malignancy. The malignant cells are "individual fighters", having no common control over them, only the available nutrients regulate their life. The order, which characterizes the healthy tissue, is lost in their malignant version, the cellular communications disappear [82]. The consequence of these is the well- recognizable pattern of cancer in pathological morphology. Fractal analysis could be used for rigorous pathologic pattern description [83]. The analysis of the fractal structures of malignancies could even indicate the stage of the disease, [84]. In the living system instead of the deterministic actions stochastic processes occur, so the predictions always have random, unpredictable elements. Due to the self-similarity and to the stationary stochastic processes of biosystems, all of those are a-priory pink-noise generators [**78**], [85], with definite autocorrelations. The autocorrelation of living effects is a clear fingerprint of their self-organizing structure, [**85**].

The missing information exchange in malignant tissues ([86]) could be reestablished by constraining information exchange by the amplitude modulation of the RF-carrier. Recently the research of amplitude modulated RF in human medicine has become very active [87] also clinical

trials have shown its progress [88]. A research has shown how AC electric field inhibits metastatic spread of solid lung tumor [89].

The proper modulation gains transport through the membrane by weak but periodic signal in stochastic resonance (Brownian-engine, ratchet, [90], [91]). The double well bifurcation in the membranes [92] causes sliding through (see Fig. 6.), it is shown experimentally too [93], [94].



a.) b.)

Figure 6. The "sliding" bistability (the Brownian ratchet, (a)), promotes oncothermia like an enzymatic process(b).

The dose of energy is crucial for all the selection steps. Applying too much energy realizes the classical hyperthermia, heats up all the components of the target; the treatment loses its selection ability. The popular wisdom is valid: the difference between the medicine and poison is the applied dose only.

8. *Thermo-electromagnetic effects at cell-membranes*

Thermal limit

The cellular membrane is a controlling layer between electrolytes orienting ionic currents in the picoampere range. Most of these effects are thermally induced, or at least competing with the thermal noise in the object. Theoretical approximations compared thermal noise fluctuations of the cell membrane field strengths to the field strengths induced at the membrane [95]. The effective field strength of thermal noise was first calculated by Weaver and Astumian [96] (W-A model). They assumed changes in the field strength are results of fluctuations of space charges on both sides of the cellular membrane, and further showed thermal noise limits at low frequencies. The model, which calculates large number of "elementary" cellular units [97], leads a white noise which does limit the external field application effectively in wide range of frequencies, except when it is spherical (zero mode noise component), [**97**]. The spherical component of noise, could overcome the thermal noise to elicit a biological effect.

Artificially, we can produce pure zero mode field indirectly by changing the extracellular matrix (ECM) composition and thus inducing ionic currents, or by heating the ECM and thus producing thermo-diffusion.

Heating of the ECM more intensively than the cytoplasm provides a spherical thermal gradient and consequently creates heat-flow through the membrane of all the selected individual cells, [98]. According to the Onsager's reciprocity relations, the induced heat-flow is coupled to charge current too, as well as the kinetics of the processes are also coupled, [99]. This current is ~150 pA/μm^2, [**98**]. This ionic current creates a zero mode electric current, which in turn induces a zero mode electric field in the cell membrane. Therefore, even small fields with zero-th mode components could elicit biological effects, despite the thermal energy noise was significantly

higher than the external electromagnetic effect [100].The temperature gradient through the cellular membrane pumps the non-equilibrium thermal processes. The gradient is quite large (~0.001 °C/nm [≈106 °C/m]), [**98**], creating a considerable heat-flow (~1.5 pW/μm^2). Due to the rigid cell membrane of the cancerous cells [101], the electro-osmotically enhanced intracellular pressure [**13**], could reach the maximal tolerable lateral tensile stress of the membrane. This significantly increases the membrane permeability, allowing the internal HSP chaperones to be expressed on the outer membrane to ignite immune reactions. This process is promoted by the temperature effect on the membrane permeability [**13**].

The RF-current anyway has special effects characteristically acting on the membrane of the cells. Its ohmic component directly affects the membrane, while the displacement current (imaginary component) deflects it [**13**], causing various mechanical effects on the outer membrane. The effect of the ohmic component is proportional with the square of the RF-current (Joule heat) while the capacitive component simply depends on the current itself.

Measurements well show the development of the natural apoptotic processes of oncothermia in HT29 xenograft model (see Fig. 7.). After the apoptosis, a special invasion ring forms where neutrophil and monocytes activity were measured. The expression of CD3, CD4 and CD8 supports expectations the abscopal (bystander) effect by oncothermia [102]. This was clinically proven too, [103].

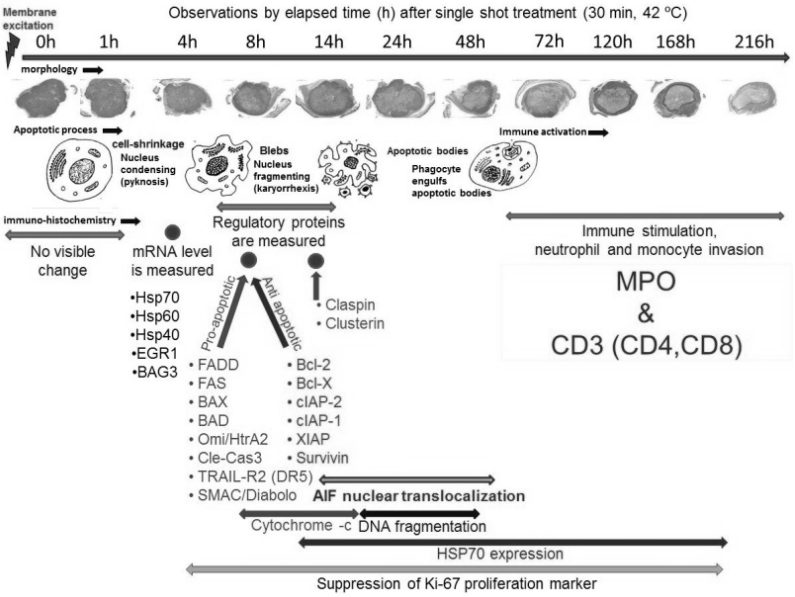


Figure 7. The measured molecular changes after the single shot (30 min) treatment by modulated electrothermia (oncothermia) (The mRNA level was measured by Affimetrix DNA chip, and the protein level was checked with Proteome Profiler Human Apoptosis Array.)

Conclusion

Clues for the success of the proper hyperthermia treatment are offered by modulated electrothermia (oncothermia). It formulated a new paradigm: [21], where we properly select the tumor (malignant lesion) as a target and act on the malignant cells especially. The physiological feedback loops could be controlled, the negative effects of the natural homeostatic control is blocked. Malignant cells are eliminated in an apoptotic way together with the action on the innate and adaptive immune system.

The problem of the misleading and uncontrollable temperature as dose is changed, calculating the physiological reaction of the patients too. The oncothermia solution answers positively on the

doubt and introduces the fourth column of the gold-standard oncological methods, additional to the surgery, radio- and chemo-therapies.

These advantages give us a possibility to put hyperthermia in its place to become a feasible and accepted modality of cancer treatment.

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