Oncothermia Journal 7:253-258 (2013)

Burden of oncothermia – Why is it special?

Oliver Szasz[1]
(1) Department of Biotechnics, Szent Istvan University, 2100-Godollo, Pater K. u. 1., Hungary
& Oncotherm GmbH, 53842-Troisdorf, Belgische Allee 9, Germany
Corresponding author: droliverszasz@gmail.com

Published: http://www.hindawi.com/cpis/medicine/2013/938689/

Burden of oncothermia – Why is it special?

Abstract

There are many contradictory opinions about conventional hyperthermia in oncology. The main points are the physical, technical imperfection of classical heating, as well as the limits of the natural physiological feedback of the organism. We would like to present the definitive differences between oncothermia conventional hyperthermia, explaining the new line of problem-solving in this important field of oncology.

Keywords: hyperthermia, oncothermia, nanotheremia, non-equilibrium, modulation

Problem

General opinion among the specialists, that the physics limits the deep heating [1]. The limit is formed by the heat-conduction and other thermodynamic factors. The imperfect thermal conditions are combined with insufficient electrodynamic facilities to concentrate the energy focused in depth. This skimpiness appears in the unwanted hot-spots and the overheated surface when the actually necessary energy is pumped through.

Some experts evaluated the situation a bit differently, blaming the biophysical, physiological factors having technic inefficiencies. According to this position the physiological negative feedbacks seeking to reestablish the thermal homeostasis are blocking the proper job, [2].

Certainly, both the physical and physiological deficiencies are involved in the hindrance of the success and probably it is accompanied with a factor of improper references also. In case of comparison of various heating methods the only one factor is measured as relevant: the temperature in the targeted volume. However, this reference has various complex shortages and could lead to misleading consequences. The high temperature ablation in a small volume for short time cannot be compared with a longer time local or regional heating or even less comparably with the whole body heating on the same temperature. When a local or regional heating reaches 41.5 °C homogeneously in the target that could be a therapeutic indicator of success, but the same homogeneous temperature reached by whole-body treatment gives completely different results, and also the expectation of the expert therapist is different. The temperature alone is not a reference point [3], because the physiological conditions modify the actual state even when the temperature is equal. Typical example is the difference of the blood-heating approaches and tissue heating ones. In blood-heating cases (e.g. limb perfusion, subcutane radiative heating), the hot blood heats up the tumor. In case of the tissue–heating the blood remains cold (stays on body temperature). This difference makes huge deviations in the thermal and physiological actions: in the first case the heat flows from the blood to the target, while in the second case it is completely the opposite. In the first case the static thermal equilibrium can be reached after a definite time, while in the second case the thermal equilibrium remains dynamic always, the heat-flow is always active from the heated volume to the other body-parts by the blood-flow. In this second case the heated volume (tumor) is a hot heat-source to heat the body up. Measurement of the intensive thermodynamic parameters (like temperature) supposes at least local equilibrium, which never could be realized due to the intensive contra-regulatory effects. (This concept however, became the main request of the classical hyperthermia approach in its guidelines.)

The forced equilibrium increases the heat-flow to the blood-stream, which is an effective cooling media trying to block the static concept. Static constrains try to block the natural dynamism of the living system, which mobilizes its forces to keep the dynamic equilibrium instead of the static one. This creates protection mechanisms of the actual status quo in the tissue, defending the tumor instead of its elimination. (These processes: like intracellular HSP development, like forced delivery of metabolic species [oxygen and nutrition], like systemic cooling control, like various stress reactions, etc.) Process reaching equilibrium mobilizes higher level of physiological contra-actions and accelerates a competition between the constrains and the nature. This falsely mobilizes the natural healing forces. (Natural actions are gained against the actual treatment and not against the "common enemy", against the malignancy.)

When the temperature is not enough then the standardly used absorbed energy (specific absorption rate; SAR), could be the solution. However, this is again problematic. Due to the variability of the blood-flow of the parts of the body, the same SAR could heat up the same volume to completely diverse temperatures. The actual blood-flow cools down the target and sinks the energy by indefinite level,

because the bloodflow is non-linearly controlled by the physiologic feedback system.
In consequence, the simple temperature characterization of the therapy has numerous problems, like

- Temperature heats up the vicinity of the tumor, it can not be kept locally focused,
- Temperature increases the danger of burn of healthy parts in depth (misfocusing, conduction, etc.),
- Temperature requests the increase of the safety-cooling on the skin,
- The increased surface cooling blocks the temperature sensing in the skin,
- The increased surface cooling makes the skin even more isolating, and so the electric burn is more likely,
- Temperature increases the blood-flow in the region, in consequence increases the dissemination,
- In complementary application with radiotherapy the forced high temperature suppresses the efficacy or blocks at all the effect of radiotherapy,
- In complementary application with chemotherapy the forced high temperature suppresses the efficacy or blocks at all the chemo-penetration into the tumor (vasocontraction or blood-vessel blockage in the tumor),
- In complementary application with chemotherapy the forced high temperature increases the cytotoxic side effects in the heated healthy tissues around by increased chemo-reaction rates (vasodilatation in the healthy tissues),
- The toxins from the necrotic cells are rapidly transported into the whole body, challenging the anyway low immune status of the patient.

Additionally to the temperature as reference we have challenges from the variation of the patient's individual behaviors. We have to calculate not only the physiology of the patient, but the psychology as well, not forgetting, that the treated body-part organ belongs to somebody. The personal differences are modified by the previous treatments and tolerances, and by the personal tolerance limits. Most of the decisions in serious cases need medical experience, we not apply automatically the prescribed protocols formulated for average patient.

Solution

The physiology is an interdisciplinary subject, it applies numerous principles and discoveries. The electronic structure approach of solid state physics (e.g. Szent-Gyorgyi, [4], [5]), the superconductivity (e.g. Cope, [6]), the electromagnetism (e.g. Liboff, [7], [8]), the thermodynamics (e.g. Schrodinger, [9], Katchalsky & Curran [10]), etc. are all parts of the physiology, and make it really complex as the phenomena of life itself is. The living organism develops itself, rearranges, reorganizes the incoming chemicals and builds up its own structure, consequently lowers the entropy. Various modern approaches are developed in the last decades on this complexity, like self-organization ([11], [12], [13], [14],), fractal physiology ([15], [16], [17], [18]), and the bioscaling ([19], [20], [21]). These modern achievements are used for solutions of the above problems of hyperthermia in oncology.
There are special biochemical and biophysical changes caused by the above differences of the malignant cells and used for oncothermia specialties:

- their extracellular matrix has different concentration of ions [22], which can be measured by positron emission tomography, PET[23];
- they have different conductive behaviors [24] which can be measured by electroimpedance tomography (EIT) [25];
- their electromagnetic environment (how they conduct the electromagnetic currents and waves) is different, [26], [27]. This can be measured by Cole-Cole impedance measurements [28].
- order of their electrolyte (aqueous solution) differs, [29]. The healthy tissue has ordered water-states [30], in extracellular matrix [31], [32], while malignancy decreases the order of the electrolyte matrix, decreasing the cell-cell adhesion promoting the proliferation [33].
- The dynamical process has special self-organization [34], forming special structures [35], [36], bioscaling [37], and noise spectrum [38], which certainly differs in cancerous state. The information to recognize the tissue is well coded in the order of those [39], [40].

The solution of the problems of conventional hyperthermia is the nanothermia, it targets the cellmembrane of the malignant tissue, and do not waste the heat (energy) to the volumes which are irrelevant in the point of view of destroying the malignant cells. This nanothermia heating (concentration of nanoscopic range of the target) is the oncothermia [41], using the distinguished points of the

differences between the malignant and healthy cells. The clue to find the mechanisms, which could create the requested optimization, selection and control of the energy intake is based on the clear biophysical differences between healthy and cancerous cells, finding the biophysical property to focus the energy on the desired cellular membranes. The hyperthermia is macro heating, it heats a given volume of the target equally, and distributes the SAR in conductive and convective ways. The result is that the heated volume will be a massive heat-source to elevate the temperature of the complete neighboring tissues, unselectively.
The efficacy of the energy depletion intended to be pumped into the tumor is limited by the energy loss outside the malignant target. The main factors of the useless energy absorptions are:

- The absorbed energy by the tissues transfers the effect to the deep-seated tumor,
- The heat-exchange by the blood-flow,
- The heat exchange by the heat-conduction from the tumor to the surroundings.

These heat-sinks modify the overall performance of the treatment and make the full heating process for the malignancy uncontrollable. The real effect, used for the intended treatment is less than the loss, and the efficacy is usually less than 25%, which is very low. The problem of this is not only that the large part of the energy is wasted, but also the useless energy part could be dangerous by overheating the healthy tissues as well as increasing the metabolic rate and also gives physiological reaction on this effect which tries to break the homeostasis [42]. The massively heated tumor volume intensifies the control of physiology, and weakens the expected effect.
The adequate corrective actions for these challenges would be the more precise targeting, decreasing the loss in the surroundings and to avoid the physiological corrections to suppress the desired effect. To construct the solution some new effects have been used to increase the efficacy:

- Apply the electric field as carrier of the energy, and that field cannot be compensated by homeostatic control.
- Apply correct microscopic targeting, using the energy-absorption cell-by-cell efficiently.
- Apply such mechanisms, which initialize natural effects to kill the malignant cells.
- Apply mechanism, which carries info for disseminated cells to be blocked.

Oncothermia uses these new approaches to fit it for the best curative performance. This new approach (the fractal physiology) is applied for oncothermia. The carrier electric field is delivering the time-fractal structure to the tissues, enhancing considerably the selection between the connected healthy cellular community and the individual autonomy of the malignant proliferation. In this application there is no considerably heat-flow to the blood-stream, no gain of the feedback of electrolyte balancing-loop. Oncothermia uses tumor killing approach, which is well fitted to the dynamism of the living system, it does not constrain for false defense. Thermal gradients make dynamism in a very local area of the cell-membrane of malignant cells. The applied selection focuses on this thermal nonequilibrium.
The applied fractal modulation [43] makes possible the selecting and supporting of the natural processes to activate the natural healing mechanisms and reestablish the healthy “social signal’ between the isolated cells, promoting the anti-malignancy collectivity. The carrier frequency delivers the information (modulation frequencies), for what the cancer cells are much less “transparent” than their healthy counterpart is. Malignant cells are heated up by the selectively absorbed energy. What makes the difference on the absorption? It is the missing collective order in malignancy. The healthy cells live collectively. They have special “social” signals [44] commonly regulating and controlling their life. They are specialized for work-division in the organism, and their life-cycle is determined by the collective “decisions”. The cancerous cells behave non-collectively; they are autonomic. They 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 disappeared [45].
By modulation the cellular connections (adherent connections, gap-junctions) of malignant cells are reestablished to avoid the further dissemination. Selection is solved on cellular level suppress the dissemination of the malignant cells. The method is similar to the process when the light goes through the windows-glass. When the glass is transparent to that specific set of colors (visible light, definite interval of frequencies), its absorption is almost zero, all the energy goes through it. However, when it has any bubbles, grains, precipitations etc. those irregularities will absorb more from the energy, their transparency is locally low, their energy absorption is high, they are heated up locally. It is a self-selection depending on the material and the frequency (color) which we apply in the given example. Cellmembrane permeability is increased by the nanothermia process, expressing the HSP on the outer

membrane signalizing the cell malignancy for the systemic immune actions. Cell-membrane is excited to ignite various communication pathways in the cells. Relatively slow "step-up" heating keeps the non-equilibrium conditions stable for long time for action. Advantage of the step-up heating protocol is that it does not create considerable physiological contraactions, the slow heating makes the healthy tissue adapted to the growing temperature, and does not generate high stress and following stress-reactions. Oncothermia is mainly regulated by the patient's tolerance. Its control is based on thermal sensing of the patients, for safety and for efficacy reasons. Safety is avoiding to burn the tissue of the subcutaneous layers, the efficacy to apply such energy, which does not overload the patient's natural defending/protective system.

Oncothermia heats the target like the fuel cells liberate the energy. The selection of malignant cells is made by their metabolic activity according to Otto Warburg [46], a Nobel-Laureate in Physiology. Warburg recognized the metabolic difference between the malignant and healthy cells: the malignant cells have much higher flux of glucose than their healthy counterparts do. The higher glucose metabolism needs larger ionic fluxes in the vicinity of the individual tumor-cells. The RF-current, which flows through the cancerous lesion, automatically focused by its lower impedance, will flow mainly in the extracellular electrolyte, because the cells are electronically capsulated (isolated) by their membrane by more than one-million V/m field-strength. (The membrane is a good isolating lipid (fatty) layer). The membrane disruption is one of the targeted aims [47], [48], [49], as well as many research groups are dealing with the electric field action on the cellular divisions [50], [51], [52], [53]. The main advantage of the electric field application is the missing control of the organism, there is no physiologic sensor and control of this effect. No physiologic feedback limits the electric field directly, only the consequences of its action could be regulated. The process made by oncothermia has its main energy delivery into the extracellular liquid, heating it up, and creating a little (1/1000 oC) difference between the inner and outer temperature of the cell. This is only a small difference, but regarding the very
tiny membrane layer (5 nm), the small difference in standard conditions is high: ~200,000 oC/m! The system is far from the thermal equilibrium [54]. This starts a prompt heat-flow from the outside to the cell through the membrane, and permanently acts till the temperature difference exists. Despite the quick heat-flow through this tiny membrane, the heat-current is long-lasting, till the full cellular interior is heated up to the same temperature as outside.
The large extracellular SAR makes not only thermal, but also electric effects in the tissue; the extracellular matrix has higher current density than the other electrolytes. The current density gradient is accompanied by the gradient of the electric field, which could reorient the high-dielectric constant proteins in the extracellular liquid. The orientation of these protein molecules would be constrained perpendicular on the membrane surface. By this effect, the lost adherent connections could be rebuilt between the malignant cells, which were indeed shown experimentally, [55]. This effect helps to suppress the metastatic dissemination as well as promoting the intercellular signals to activate the natural cell-killing mechanisms.
Development of the thermo-tolerance, such as heat-shock protein (HSP) production [56], is one of the suppressors success of hyperthermia, [57]. From the point of view of the thermo-tolerance, one of the most prominent chaperone proteins is the HSP72. The concentration of this HSP is 5-10 times lower in the healthy cells than in the malignant ones, [58]. However, responding to the heat treatment, their concentration in healthy cells became 8-10 times higher, while the same heat treatment of the HSP72 multiplication creates only 1.2-1.5 times higher concentrations in malignant cells, [58]. Oncothermia is a highly personalized, energy-dose dependent, nano-scale heating technology, which can solve all the debated problems of the conventional hyperthermia. Oncothermia uses higher thermal load on cellular membrane than any other hyperthermia can do, but its physiological feedback remains low, due to the nano-scale capability of the treatment. Also the excited apoptotic pathways, reestablished adherent connections and controlled abscopal effect makes the job.

Oncothermia is personalized; the heat delivery has numerous important physiological controls. The objectivity of the treatment definitely depends on the radiofrequency current and its gained voltage on the given impedance on the tumor. This current is well-regulated by the skin-conductance and by the connected physiological changes. The inconvenient feeling of RF-heating defines a pain-limit, which depends on many objective and individual factors. A good approach is to regard the nerve-cell sensitivity objective (the cellular processes are well unified), and regard the personal differences as influence of physiological factors. The main factor for heat-sensitivity are the blood-perfusion and blood-flow in the subcutaneous layers where the heat-sensing nerves are located. The high blood-flow is an effective heat

exchanger, it cools the given volume, and the nerves tolerate higher energy-flow through the layer. The high blood cooling is not only the facility to have higher energy-flow, but also to get more current through the volume. The higher current density excites the nerve-sensing, and the feeling again is an overheating, requests down-regulation. In case of low blood-perfusion the current is small, so the nerves can tolerate more intensities than in any other situations. The crucial point is the surface heat-regulation, which has to be carefully done by the electrode systems. When the surface temperature is kept constant, the nerves mainly regulate the current density, which is the clue of the objective regulation. A detailed mathematical model has been worked out for this regulation mechanism, and applied in oncothermia treatment.

The other factor is connected to the psychological interaction with the treatment process as well. In any protocols, when the temperature is described as a dose, then the required temperature cannot be achieved. Then of course it is forced by the power, so the incident energy is not limited in this case. In fact, the opposite reaction has to happen: if the patients cannot tolerate the prescribed power (and required temperature), then a lower one has to be applied. The pain in the body depth is independent of the temperature sensing nerves, the pain there has other mechanisms, which are not part of the prevention of damage (like the temperature sensing), but sensing the actual damage itself. Consequently, blocking the surface heat sensors is a high risk factor, which is never made in oncothermia therapies.

While the temperature has physiological blood-flow response, the current (electric field) has no such homeostatic regulation, it has only pain-response from the skin. This pain tolerance is constant (saturated) at 13.56 MHz [59]. This allows an objective pain sensing by the current, which depends on the thickness of the adipose layer. This creates negative feedback signal: when the fat is thick, the temperature grows and makes a temperature pain limit which increases the blood-flow by vasodilatation by step-up heating. The current in this way grows, but when the blood-conductance becomes too high, the pain from the current will limit the process again, and controls the personal merit, which is pretty objective due to the saturation of the current sensing.

Conclusion

Oncothermia is a feasible method to treat any solid malignant tumors, irrespective its primary or secondary status and irrespective of the advanced stage of the disease. The only two parameters which are considered as useful for measuring the treatment efficacy: the survival time and the quality of life.

References

[1] Nielsen OS, Horsman M, Overgard J (2001) A future for hyperthermia in cancer treatment? European Journal of Cancer 37(13):1587-1589

[2] Osinsky S, Ganul V, Protsyk V et al (2004) Local and regional hyperthermia in combined treatment of malignant tumors: 20 years experience in Ukraine. The Kadota Fund International Forum, Awaji Japan, 15-18 June 2004

[3] Fatehi D, van der Zee J, van der Wal E et al (2006) Temperature data analysis for 22 patients with advanced cervical carcinoma treated in Rotterdam using radiotherapy, hyperthermia and chemotherapy: a reference point is needed. Int J Hyperthermia 22:353-363

[4] Szent-gyorgyi A. (1941) Towards a new biochemistry? Science 93(2426):609-611

[5] Szent-gyorgyi A (1946) Internal photo-electric effect and band spectra in proteins. Nature 157:875-875

[6] Cope, F.W.: Evidence from activation energies for superconductive tunneling in biological systems at physiological temperatures. Physiol Chemistry & Physics 3, 403-410 (1971)

[7] Liboff, A.R.: Geomagnetic cyclotron resonance in living cells. J. Biol. Phys. 13(4), 99-102 (1985)

[8] Liboff AR (2003) Ion Cyclotron Resonance in Biological Systems: Experimental Evidence. In: Stavroulakis P (ed) Biological Effects of Electromagnetic Fields, Springer Verlag, Berlin-Heidelberg, pp 6-113

[9] Schrodinger E (1967) What is life? Cambridge University Press, Cambridge, United Kingdom

[10] Katchalsky A, Curran PF (1967) Non-equilibrium thermodynamics in biophysics. Harward University Press, Cambridge, MA, USA

[11] Haken, H.: Self-Organization and Information. Phys. Script. 35(3), 247-254 (1987)

[12] Sornette D (2000) Chaos, Fractals, Self-Organization and Disorder: Concepts and Tools. Springer Verlag, Berlin-Los Angeles

[13] Walleczek J (ed) (2000) Self-organized biological dynamics & nonlinear control. Cambridge Univ. Press, Cambridge

[14] Kauffman SA (1993) The Origins of Order: Self-Organization and Selection in Evolution. Oxford University Press, New York, Oxford

[15] Deering W, West BJ (1992) Fractal physiology. IEEE Engineering in Medicine and Biology 11(2):40-46

[16] West BJ (1990) Fractal Physiology and Chaos in Medicine. World Scientific, Singapore, London

[17] Bassingthwaighte, J.B., Leibovitch, L.S., West, B.J.: Fractal Physiology, Oxford Univ. Press, New York, Oxford (1994)

[18] Musha, T., Sawada, Y. (eds.): Physics of the living state. IOS Press, Amsterdam (1994)

[19] Brown JH, West GB (eds) (2000) Scaling in Biology. Oxford University Press, Oxford

[20] Brown JH, West GB, Enquis BJ (2005) Yes, West, Brown and Enquist's model of allometric scaling is both

mathematically correct and biologically relevant. Functional Ecology 19(4):735 –738
[21] West GB, Brown JH (2005) The origin of allometric scaling laws in biology from genomes to ecosystems: towards a quantitative unifying theory of biological structure and organization. Journal of Experimental Biology 208:1575-1592
[22] Heiden MGV, Cantley LC, Thompson CB (2009) Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. Science 324(5930):1029-1033
[23] Oehr P, Biersack HJ, Coleman RE (eds) (2004) PET and PET-CT in Oncology. Springer Verlag, Berlin-Heidelberg
[24] Loewenstein WR (1999) The touchstone of life, Molecular information, cell communication and the foundations of the life. Oxford University Press, Oxford, New York, pp 298-304
[25] Osypka, M., Gersing, E.: Tissue impedance spectra and the appropriate frequencies for EIT. Physiological Measurement 16, A49-A55 (1995)
[26] Szentgyorgyi, A. (1980) The living state and cancer. Physiological Chemistry and Physics 12, 99-110 (1980)
[27] Szentgyorgyi A. (1968) Bioelectronics: a study in cellular regulations, defense and cancer, Academic Press, NY
[28] Cole, K.S., Cole, R.H.: Dispersion and absorption in dielectrics. I. Alternating current characteristics. J. Chem. Phys. 9, 341-351 (1941)
[29] Damadian R (1971) Tumor detection by nuclear magnetic resonance. Science 171(3976):1151-1153
[30] Pauling L (1959) The structure of water. In: Hadzi D, Thompson H (eds) Hydrogen bonding, Pergamon Press Ltd, London, pp 1-6
[31] Hazlewood CF, Nichols BL, Chamberlain NF (1969) Evidence for the existence of a minimum of two phases of ordered water in skeletal muscle. Nature 222(195):747–750
[32] Hazlewood CF, Chang DC, Medina D et al (1972) Distinction between the Preneoplastic and Neoplastic State of Murine Mammary Glands. Proc Natl Acad Sci USA 69(6):1478-1480
[33] Szentgyorgyi A. (1977) The living state (1977) Proc Natl Acad Sci U S A. 74(7): 2844–2847.
[34] Walleczek J (ed) (2000) Self-organized biological dynamics & nonlinear control. Cambridge Univ. Press, Cambridge
[35] West BJ (1990) Fractal Physiology and Chaos in Medicine. World Scientific, Singapore, London
[36] Bassingthwaighte, J.B., Leibovitch, L.S., West, B.J.: Fractal Physiology, Oxford Univ. Press, New York, Oxford (1994)
[37] Brown JH, West GB (eds) (2000) Scaling in Biology. Oxford University Press, Oxford
[38] Musha, T., Sawada, Y. (eds.): Physics of the living state. IOS Press, Amsterdam (1994)
[39] Haken, H.: Self-Organization and Information. Phys. Script. 35(3), 247-254 (1987)
[40] Sornette D (2000) Chaos, Fractals, Self-Organization and Disorder: Concepts and Tools. Springer Verlag, Berlin-Los Angeles
[41] Szasz A, Szasz N, Szasz O, (2010) Oncothermia – principles and practices, Springer, Heidelberg Dordrecht
[42] Hegyi G, Vincze G, Szasz A, (2012) On the dynamic equilibrium in homeostasis, Open Journal of Biophysics, 2:64-71
[43] Szasz O., Andocs G., Meggyeshazi N., Szasz A.: Modulation effect in oncothermia, XXXI. Conference of the International Clinical Hyperthermia Society (ICHS), 12-14 October, 2012. Budapest, Hungary
[44] Raff MC (1992) Social controls on cell survival and death. Nature 356(6368):397-400
[45] Loewenstein WR, Kanno Y (1967) Intercellular communication and tissue growth. The Journal of Cell Biology 33(2):225-234
[46] Otto H. Warburg, The Prime Cause and Prevention of Cancer accessed October 30, 2007
[47] Barnes F, Kwon Y (2005) A theoretical Study of the Effects of RF Fields in the vicinity of membranes. Bioelectromagnetics 26: 118-124
[48] Groves JT, Boxer SG, McConnell MH (1997) Electric field-induced reorganization of two-component supported bilayer membranes. Proc. Natl. Acad. Sci. USA 94:13390-13395
[49] Groves JT, Boxer SG, McConnell HM (1998) Electric field-induced critical demixing in lipid bilayer membranes. Proc. Natl. Acad. Sci. USA 95:935-938
[50] de Pomerai DI et al (2002) Growth and maturation of the nematode Caenorhabditis elegans following exposure to weak microwave fields. Enzyme and Microbial Technology 30:73-79
[51] de Pomerai DI et al (2003) Microwave radiation can alter protein conformation without bulk heating. FEBS Letters 543:93-97
[52] Zhao M, Forrester JV, McCaig CD (1999) A small, physiological electric field orients cell division. Proc. Natl. Acad. Sci. USA 96:4942-4946
[53] Kirson ED et al (2004) Disruption of cancer cell replication by alternating electric fields. Cancer Research 64:3288-3295
[54] Szasz A, Andocs G, Szasz O, Vincze G, Koncz T, Balogh L (2009) Effects far from equilibrium in electromagnetic heating of tissues. Annual Congress of Bioelectromagnetic Society, BEMS, Davos, Switzerland, June 14-19, 2009
[55] Andocs G, Meggyeshazy N (2010) Experimental oncothermia in nude mice xenograft tumor models 1t International Oncothermia Symposium, Cologne, November 22-23
[56] Bukau B, Horwich AL (1998) The HSP70 and HSP60 chaperone machines. Cell, 92:351-366
[57] Xu M, Wright WD, Higashikubo R, Roti Roti JL (1996) Chronic Thermotolerance with Continued Cell Proliferation. Int. Journal of Hyperthermia 12:645-660
[58] Watanabe M, Suzuki K, Kodama S, Sugahara T (1995) Normal human cells at confluence get heat resistance by efficient accumulation of hsp72 in nucleus. Carcinogenesis 16:2373-2380
[59] Reilly JP (1998) Applied Bioelectricity. From Electrical Stimulation to Electropathology. Springer, New York, Berlin, Heidelberg