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# The Effect of Spatially Inhomogeneous Electromagnetic Field and Local Inductive Hyperthermia on Nonlinear Dynamics of the Growth for Transplanted Animal Tumors

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## 1. Introduction

Cancer is often characterized as a chaotic, poorly regulated growth. Cancer can be viewed as a complex adaptive system. Complex adaptive systems can be described mathematically by nonlinear (chaos) theory including asymmetry, fractal structure and autocorrelation factor (Cramer, 1993). Atypical shape of tumor cells and chaotic structures of blood flow is one from characteristic of cancer process. Atypical change of cell shape in conglomerates of tumor cells and structure of blood flow is accompanied by increase of deterministic chaos (Baish & Jain, 2000; Orel & Dzyatkovskaya, 2000). Complex natural phenomena such as cancer are dynamical systems whose state changes by perturbation. The concept of deterministic chaos is hierarchical for host in contemporary ideas about role of chaos for potential application in oncology (Sedivy & Mader, 1997; Blazsek, 1992). The authors introduced concepts related to chaos theory, such as attractors, fractals and the Lotka-Volterra equations, as potentially useful approaches to allow for the analysis of carcinogenic biological processes as related to selection and competition. In certain situations, these equations give chaotic, non-linear, and nonpredictable results. Given what is known about the enormous complexity of the carcinogenic process, use of models such as these may be perfectly justified, and might provide the theoretical framework that is so desperately needed in this age of data overload to make real progress in the understanding of human carcinogenesis (Garte, 2003).

Entropy is a measure of disorder. The thermodynamic entropy of a cancerous cell is different from that of a normal cell due to the more disordered structure of the cancerous cell. The reversal of entropy flow in tumour tissues may halt tumour development due to reversed signal transmission in the tumour-host entity. This thermodynamic approach may help in the design of cancer therapy (Molnar et al., 2009).

Transplanted animal tumors which can only be experimentally induced by transplanting living tumor cells significant influence on complex adaptive systems include developing of tumor formation for experimental animals. During recent years there has been increasing public concern on potential cancer risks from radiofrequency radiation emissions (Hardell &

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Sage, 2008). Inhomogeneous pulsing electromagnetic fields (EF) stimulation of biological tissue was associated with the increase in the number of cells and/or with the enhancement of the cellular differentiation (Diniz et al., 2002). Inhomogeneous (asymmetric) and sinusoidal EF can cause different changes in protein synthesis of cells. It should be noted, that pulsed asymmetric EF and heat shock produced different patterns of polypeptide synthesis (Goodman & Henderson, 1988). Inhomogeneous pulsing EF caused significant reductions in osteoclast formation of tumor necrosis factors, interleukins (Chang et al., 2004) and in osteoblast-like cell of proliferation and gene expression (De Mattei et al., 2005). These observations provide evidence that in vitro inhomogeneous EF affects the mechanisms involved in cell proliferation and differentiation.

Magnetic resonance images demonstrate that malignant tumor can be inhomogeneous media for spatially inhomogeneous EF (Fig. 1). Cancer patient exhibited higher values within the spread parameter  $S$  range than healthy individual (Fig.2). Each wavefront will be continued independently by an arbitrary inhomogeneous structure of tumor. Propagation of inhomogeneous radio waves in tumor is accompanied by nonlinear effects with greater changes in direction and energy of electromagnetic field than in normal tissues (Kattapuram et al., 1999).

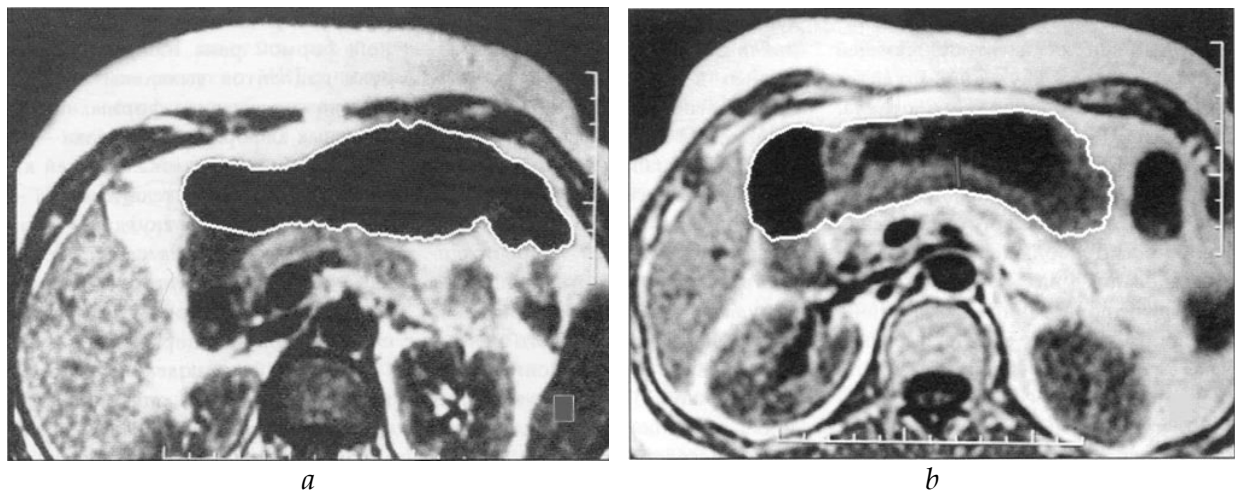


Fig. 1. T1-weighted MR images of the stomach: *a* - healthy individual; *b* - cancer

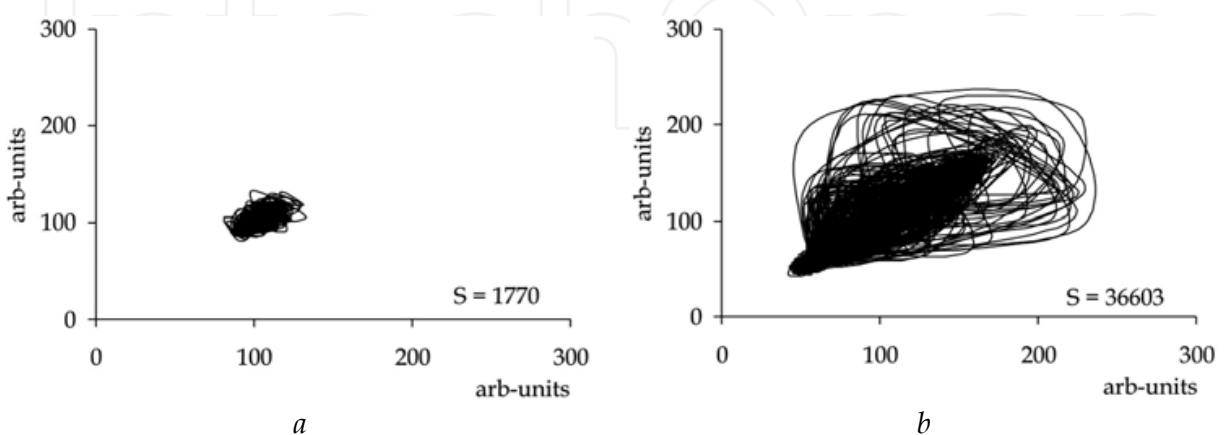


Fig. 2. Phase map of T1-weighted MR images of the stomach: *a* - healthy individual; *b* - cancer

The complete wave field at a tumor will be then obtained as an integral superposition of all wavefront arriving in some neighbourhood of the object. Inhomogeneous electromagnetic wave can be written from Maxwell's equations in the form of an inhomogeneous electromagnetic wave equation (or often "nonhomogeneous electromagnetic wave equation") (Purcell, 1985). Relationships between transplanted animal tumors and external inhomogeneous EF that initiated in them local hyperthermia are important for understand of the principles nonlinear dynamics in cancer process and multimodal approach (and typically nonlinearly) for him treatment (Furusawa & Kaneko, 2000).

Doxorubicin (DOXO) is an anthracycline quinone antineoplastic antibiotic that has been shown to have a wide spectrum of clinical activity against a variety of solid tumors. The mechanisms of DOXO-induced cytotoxicity have been extensively studied and have been shown to include free radical formation and absorption of DOXO into the double helix of DNA resulting in topoisomerase II-mediated DNA damage. DOXO also causes depolarization of the membrane lipid bilayer in different cancer cell lines (Reszka et al., 2001).

Current forms of DOXO are highly toxic to the patient and can cause systematic complications, most notably cardiotoxicity. Systemic toxicity can seriously decrease the effectiveness of the drug since a lower dose must be administered to avoid toxicity. Another approach to avoid toxicity include targeted delivery, however, it is often difficult to ensure that the chemotherapy targets only the cancer tissue and the agent is localising in the target tissue. Therefore in several studies DOXO was combined with electromagnetic hyperthermia with an aim at enhancing antitumor efficacy of the drug (Shen et al., 2008). However, the cytotoxicity of this antitumor agent is increased by elevated temperatures as shown in vitro and in vivo (Marmor, 1979; Chen et al., 2004). Nonetheless, studies of DOXO and electromagnetic hyperthermia are still controversial and often show no synergism or synergism only at the doses that cannot be tolerated by subjects (Gaber, 2002). Positive clinical results of combined treatment with DOXO and electromagnetic hyperthermia are still unsatisfactory. Widespread clinical application of electromagnetic hyperthermia in the patients is limited because temperatures in the range of 41–50°C produce heat shock proteins and initiate drug resistance (thermoreistant) in tumor cells (Roemer, 1999).

Drug resistance is the single most important cause of cancer treatment failure and carries a massive burden to patients, healthcare providers, drug developers and society. It is estimated that multi drug resistance plays a major role in up to 50% of cancer cases. Today, most drug therapies involve multiple agents, as it is almost universally the case that single drugs (or single-target drugs) will encounter resistance. Drug resistance presents some of the greatest challenges to the treatment and eradication of cancer. There are many studies and reports on drug resistance in cancer cells. P-glycoprotein, the expression product of the MDR-1 gene, is strongly associated with both *de novo* and acquired resistant. The protein function as a transmembrane drug efflux pump, transporting cytostatic agents. Glutathione and its dependent enzymes may be involved in resistance to drug by providing cellular protection against free radicals damage. Resistance to drug occurs when the damaged DNA undergoes excision repair. It is likely that many mechanisms of DOXO resistance exist and that such mechanisms are cell specific. Thus, problems related to the development multidrug resistance have led researchers to investigate alternative forms of administering DOXO for treatment of cancer.

One of complex approach may be in use of inhomogeneous pulsing EF for treatment of drug resistance tumor (Miyagi et al., 2000). Pulsing EF used for stimulation of antiresistant nonthermal effect in mouse osteosarcoma cell line (Hirata et al., 2001). It is known that

exposure to the pulsing EF causes depolarization of cell membranes and modifies drug resistance of tumor cells (Pasquinelli et al., 1993; Ruiz-Gómez et al., 2002).

One of the branches in electromagnetic hyperthermia known as inductive hyperthermia (IH) is based on the use of magnetic and electric components of EF in the radiofrequency spectrum for the localization and the concentration of heat during anticancer neoadjuvant therapy or activation of susceptor material implanted in the tumor. The equivalent power density (power density of the plane wave having the same field intensity) for magnetic field is greater than that for the electric field by a factor of ten (Martino, 1962; Moseley, 1988).

During IH of tumor the process of irradiating realize by near-field. In the near-field the maxima and minima of electric and magnetic fields do not occur at the same points along the direction of propagation as they do in the case of the far-field. In this region, the electromagnetic field structure may be highly spatially inhomogeneous and typically, there may be substantial variations from the plane wave impedance i.e., in some regions, almost pure electric fields may exist and, in other regions, almost pure magnetic fields (Jordan & Balmain, 1968). The magnetic component of EF causes heating in tumor tissues through induced eddy currents. Incorporation of antitumor agents into the tumor cells is increased by eddy current stimulation, which is induced by pulsing magnetic fields. Therefore, the cell cycle shifts from the non-proliferative to proliferative phase that leads to increased antitumor activity of the drug (Ivkov et al., 2005; Jin et al., 1998; Orel et al., 2005).

It is well known that EF can influence the chemical reactions to raise their activation energies above threshold levels of thermal noise (Weaver et al., 1999). Nonthermal effects can reduce existing disadvantages on all of the classical thermal treatment (Blank & Soo, 2001; Longo & Ricci, 2007).

In paper (Boddie et al., 1987), it was suggested to produce an inhomogeneous EF pattern with eddy current orthogonal to the magnetic force lines during regionally-focused hyperthermia of a tumor. Really, it is possible to suppose that increased inhomogeneity of EF will activate a non-equilibrium thermodynamical process in a tumor and increase antitumor activity of DOXO. Separately nonthermal and hyperthermal effects (41–50°C) of amplitude-frequency modulation for initiation EF inhomogeneity during treatment of animal tumor is generally used. However, the influence of spatial inhomogeneity of EF and local IH in the range physiological hyperthermia (37–40°C) on nonlinear dynamics of animal tumor growth hasn't been well enough studied yet.

This paper examines the effects of spatially inhomogeneous EF, local IH in the range physiological hyperthermia on nonlinear dynamics of the growth for transplanted animal tumors and entropic action during treatment by DOXO of DOXO-resistant Guerin's carcinoma.

## **2. Materials and methods**

### **2.1 Experimental animals**

In the study, 180 male rats weighing  $170 \pm 20$  g bred in the vivarium of National Cancer Institute and 20 C57BL/6 male mice weighing  $19 \pm 1$  g bred in the vivarium of Bohomolets Institute for Physiology Research, NAS of Ukraine (Kyiv, Ukraine) were used.

### **2.2 Tumor transplantation**

The transplantation of Guerin carcinoma, Lewis lung carcinoma, sarcoma 45, Walker 256 carcinosarcoma and Pliss lymphosarcoma were performed according to the established

procedure. All animal procedures were carried out according to the rules of the regional ethic committee. Animals were housed in 2 groups: group 1 – control (no treatment); group 2 – irradiation by elliptic applicator with straight profile (ASP) (40 MHz).

DOXO-resistant Guerin's carcinoma was acquired according to (Solyanik et al., 1999). Thirty sequential subcutaneous transplantations of Guerin carcinoma cells ( $3 \cdot 10^6$  per animal) received from DOXO-treated rats. The transplantation of DOXO-resistant Guerin's carcinoma was performed subcutaneously by standard method into the right hind leg. Animals were housed in four groups: 1 – control (no treatment); 2 – DOXO-administration; 3 – DOXO-administration + electromagnetic irradiation (EI) by ASP; 4 – DOXO-administration + EI by elliptic applicator with the circular arc in profile (AAP). Each group contained ten animals.

### 2.3 Electromagnetic irradiation

First prototype of the device for medical treatment called “Magnetotherm” (Radmir, Ukraine) was used (Nikolov et al., 2008). The frequency of EI was 40 MHz with an initial power of 100 W. The animal tumors irradiated locally (Fig. 3) by inductive coaxial applicators that had differed by the geometry and spatial inhomogeneity of EF.



Fig. 3. Electromagnetic irradiation of animal tumors

ASP was an ellipse on a horizontal plane with the semi-axes  $1.5 \times 2.5$  cm and straight profile (Fig. 4a). AAP profile was an arc of the circle with the radius 2.3 cm (Fig. 4b) (Ares et al., 1996).



Fig. 4. Appearance of inductive applicator: *a* – ASP; *b* – AAP

EF distribution was computed according to (Mittra, 1973) (Fig. 5). Spatial inhomogeneity of EF was estimated by asymmetry parameter of electric  $a_E$  and magnetic  $a_H$  field strength distribution according to (Korn & Korn, 1968). Animal tumor was positioned in the center of applicator loop at the distance 0.3 cm from tumor surface. Specific adsorption rates (SAR) of EI were calculated according to (Mittra, 1973). Similar design was used in helical field stellarator for the plasma to increase entropy of EF (Weller et al., 2001).

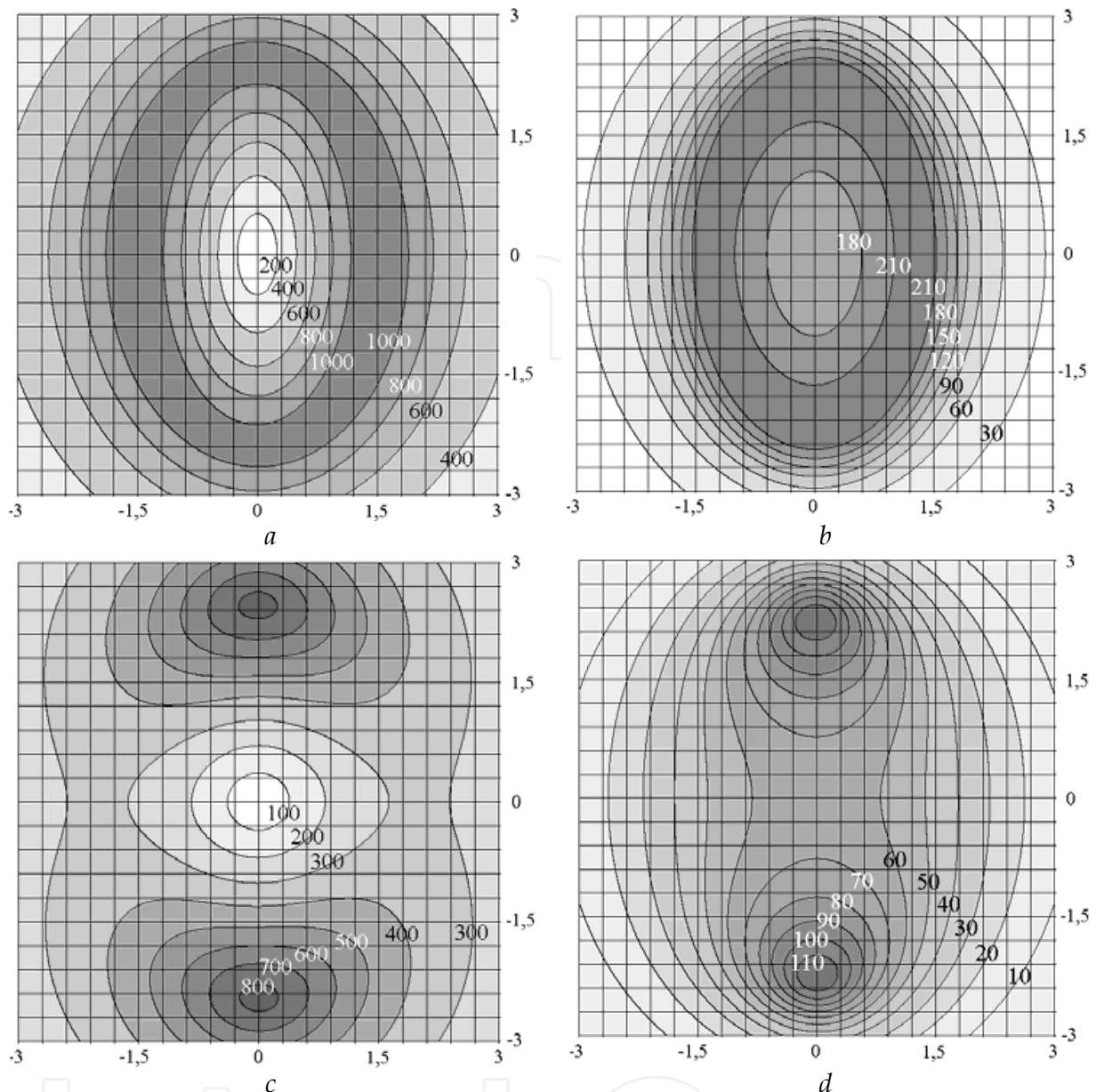


Fig. 5. The isolines of the electromagnetic field: *a* – ASP, electrical component with  $a_E = -0.03$  a.u.; *b* – ASP, magnetic component with  $a_H = 0.16$  a.u., SAR = 8.8 W/kg; *c* – AAP, electrical component with  $a_E = 0.89$  a.u.; *d* – AAP, magnetic component with  $a_H = 0.48$  a.u., SAR = 1.6 W/kg. Distance to the plane of applicator was 0.5 cm; the values on isolines indicated the tension of the electrical field in V/m and the magnetic field in A/m; the distance in cm is indicated on the axis of abscissas and ordinates

The change of thermal pattern on surface of phantom from fatty tissue of the pig after irradiated by EF shown in Fig. 6. The structure of heat formation on the surface of phantoms depends on the degree of electromagnetic field nonuniformity and it is similar to computed.

#### 2.4 Treatment of animals with doxorubicin-resistant Guerin's carcinoma

Experimental animals were treated by DOXO (Pharmacia & Upjohn) in the dose 1.5 mg/kg. The treatment was performed five times by DOXO and EI from 10 to 18 days after tumor transplantation every other two days. Tumor volume before treatment was  $0.43 \pm 0.05$  cm<sup>3</sup>.

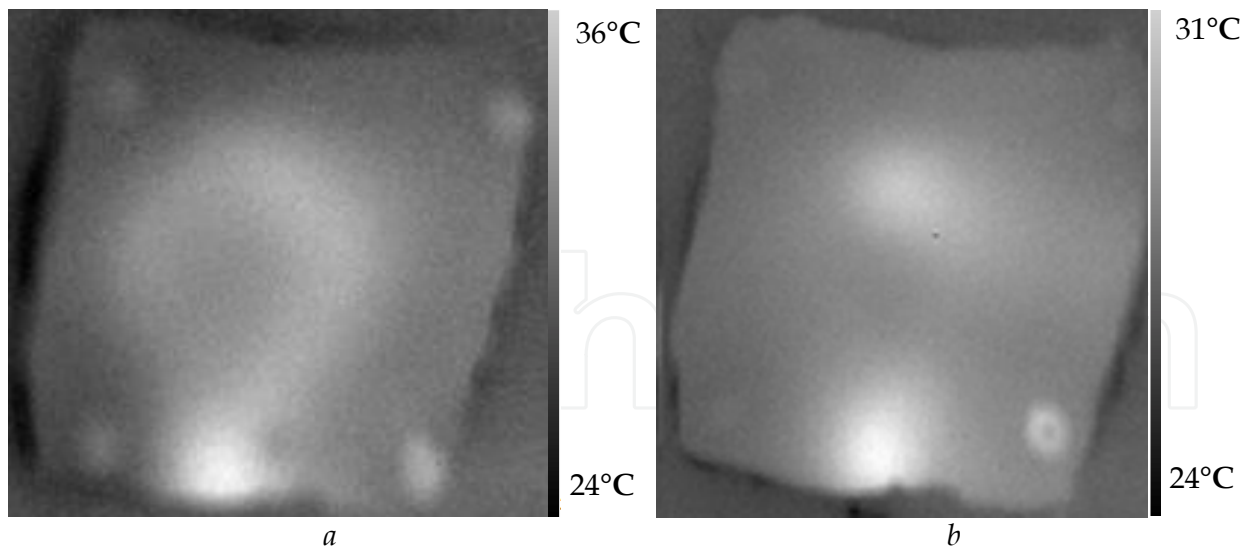


Fig. 6. The change of thermal pattern on surface of phantom from fatty tissue of the pig after irradiated by: *a* -ASP; *b* - AAP

### 2.5 Temperature studies

The temperature was measured in the tumor centre of DOXO-resistant Guerin’s carcinoma by the fiber-optic thermometer TM-4 (Radmir, Ukraine). The kinetics of typical temperature changes for animal tumor under EI is represented in Fig. 7.

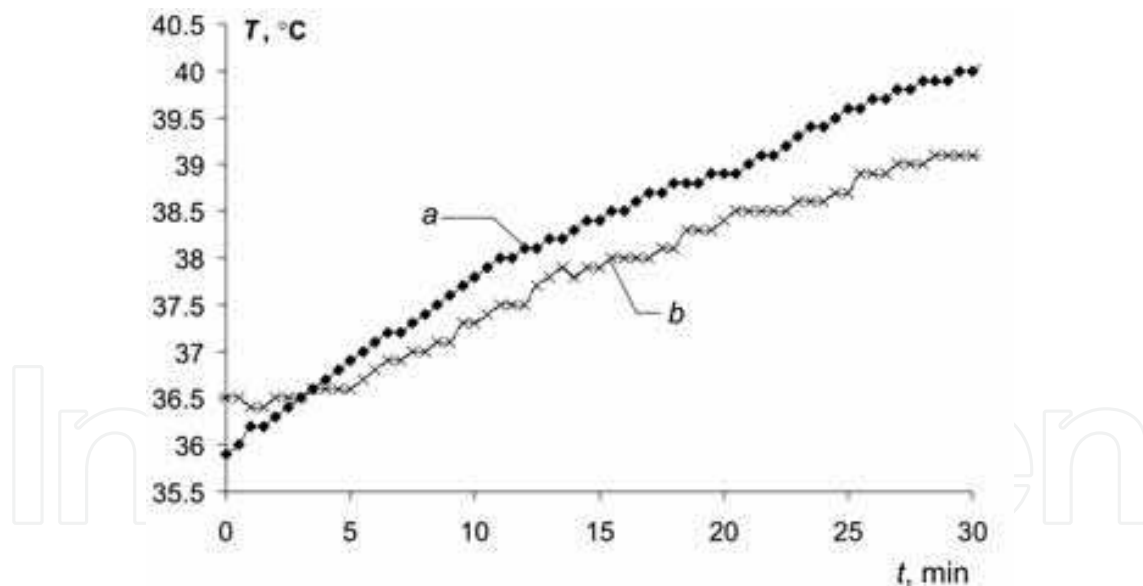


Fig. 7. The temperature changes in the centre of DOXO-resistant Guerin’s carcinoma during EI by ASP (*a*) and AAP (*b*)

The temperature was reached up to 39.1°C after 15 min and 40°C after 30 min EI by ASP, as for AAP that was 37.9 and 38.4°C, accordingly. The time between two measurements was 4 hours. It is necessary to notice, that tumor temperature was slightly increased after EI by ASP in comparison with AAP. The kinetics of temperature growth in the tumor was quasilinear. The fluctuations of experimental values evaluated by standard error of temperature in linear regression model. The standard error was 0.15°C for ASP and 0.1°C for AAP.



Preliminary research showed that 15 and 30 minutes of local EI on conventional Guerin carcinoma initiated practically identical strengthening of DOXO antineoplastic activity. Therefore, with aim of milder hyperthermic non-equilibrium effects at physiological temperatures the irradiation was being performed during 15 minutes at once after treatment by DOXO.

The animals were immobilized on the special panel to indicate the heat generation pattern of EF. The thermography was conducted by remote thermograph (B.E. Loshkarev Institute of semiconductors of NAS of Ukraine). The inhomogeneity structure of digital thermograms was estimated by the Shannon entropy ( $S$ ) equation meant for a statistical measure of the disorder (non-equilibrium of thermodynamical process) of a system (Korn & Korn, 1968).

## 2.6 The analysis of nonlinear kinetics of tumor volume

Nonlinear kinetics of tumor volume was evaluated by growth factor  $\varphi$  according to autocatalytic equation:

$$\frac{dx}{dt} = \varphi(x + x_0)(1 - x), \quad (1)$$

where  $x = \frac{\Phi - \Phi_0}{\Phi_\infty - \Phi_0}$  is relative tumor growth by time  $t$ ;  $x_0 = \frac{\Phi_0}{\Phi_\infty - \Phi_0}$  is relative tumor

volume at the moment of time  $t = 0$ ;  $\Phi_0$  and  $\Phi_\infty$  is initial and limiting tumor volume accordingly;  $\Phi$  is tumor volume at the moment of time  $t$  (Emanuel, 1977).

The solution of equation (1) is

$$\Phi = \Phi_0 + \Phi_\infty \cdot \frac{e^{\frac{\varphi \Phi_\infty}{\Phi_\infty - \Phi_0} t} - 1}{1 + \frac{\Phi_0}{\Phi_\infty - \Phi_0} \cdot e^{\frac{\varphi \Phi_\infty}{\Phi_\infty - \Phi_0} t}}. \quad (2)$$

The effect of EF and local IH on nonlinear dynamics of the growth of animal tumors was evaluated with the braking ratio:

$$\kappa = \frac{\varphi_c}{\varphi_{EI}}, \quad (3)$$

where  $\varphi_c$  - is growth factor for control group of animals,  $\varphi_{EI}$  - is growth factor for group after EI.

## 2.7 The heterogeneity of tumor structure in ultrasound image

Ultrasonic studies were done before and right after EI by ultrasonic apparatus ATL HDI 3000 (Fillips, USA) with the use of 6 MHz transducer. During ultrasonic studies the transducer was stationary fixed relative to animal tumor.

The heterogeneity of ultrasound image  $G$  in tumor tissues for studies of tumor vessels was evaluated with spatial autocorrelation statistics  $r$  by Moran (Bailey & Gatrell, 1995; Orel et al., 2007a):

$$G = 1 - r, \quad (4)$$

$$r = \frac{n \sum_{i=1}^n \sum_{\substack{j=1 \\ i \neq j}}^n w_{ij} (x_i - \bar{x})(x_j - \bar{x})}{\left( \sum_{i=1}^n (x_i - \bar{x})^2 \right) \sum_{i=1}^n \sum_{\substack{j=1 \\ i \neq j}}^n w_{ij}} \tag{5}$$

where  $n$  is the number of pixels in selected region of interest in ultrasound image,  $x_i$  is the intensity of  $i^{\text{th}}$  pixel,  $\bar{x}$  is the mean intensity of whole region of interest, and  $w_i$  is a distance-based weight which is the inverse distance between pixels  $i$  and  $j$  ( $1/d_{ij}$ ).

### 2.8 Statistical and correlation analysis

Statistical processing of numerical results was carried out using Statistica 6.0 (© StatSoft, Inc. 1984–2001) computer program with parametric Student’s  $t$ -test. Correlation analysis was performed with the MATLAB 7.0 (©1984–2004 The MathWorks, Inc.) software.

## 3. Results

### 3.1 Changes in nonlinear dynamics of the growth for animal tumors under the influence of spatially inhomogeneous electromagnetic field and local inductive hyperthermia

As it is shown in table 1 the growth kinetics of animal tumors had very different nonlinear responses under the influence of spatially inhomogeneous electromagnetic fields ( $a_E = -0.03$  a.u.;  $a_H = 0.16$  a.u.) and local IH initiated by ASP. The strongest inhibition effect under the influence of EI was in Pliss lymphosarcoma and sarcoma 45. The growth stimulation of animal tumors after EI was recorded in Walker 256 carcinosarcoma. Animal tumors for Lewis lung carcinoma grew nonsignificantly but average number of metastases on a mouse in the lungs was increased on 86%. Nonlinear dynamics of tumors’ growth was much differed for each single animal in all investigated groups.

EI of Gueren carcinoma by AAP with inhomogeneous electromagnetic fields ( $a_E = 0.89$  a.u.;  $a_H = 0.48$  a.u.) statistically not significant changed nonlinear dynamics of malignant growth in comparison with control group of animal without treatment.

Tumor	Parameters		
	$\varphi_c, \text{day}^{-1}$	$\varphi_{EI}, \text{day}^{-1}$	$\kappa$
Guerin carcinoma	$0.45 \pm 0.01$	$0.46 \pm 0.05$	0.99
Lewis lung carcinoma	$0.39 \pm 0.02$	$0.36 \pm 0.01$	1.07
Sarcoma 45	$0.60 \pm 0.03$	$0.45 \pm 0.01^*$	1.31
Walker 256 carcinosarcoma	$0.60 \pm 0.01$	$0.66 \pm 0.01^*$	0.91
Pliss lymphosarcoma	$0.42 \pm 0.02$	$0.32 \pm 0.01^*$	1.32

\* Statistically significant difference from control group

Table 1. The growth kinetics of animal tumors

The ultrasonic studies were used for interpretation of peculiarities in tumor blood flow during EI. Guerin carcinoma only was researched because there were problems in

visualization of ultrasound images on the monitor for other experimental tumors. Fig. 8 shows the sonogram of Guerin carcinoma on the 10<sup>th</sup> day after tumor transplantation before and after EI. The sonograms show that tumor heterogeneity parameter  $G$  for Guerin carcinoma was higher in 2.9 times after EI than without irradiation. This is in accordance with well known medical observations that EI and mild hyperthermia in tumor is characterized by intensive tumor blood flow (Song et al., 2005).

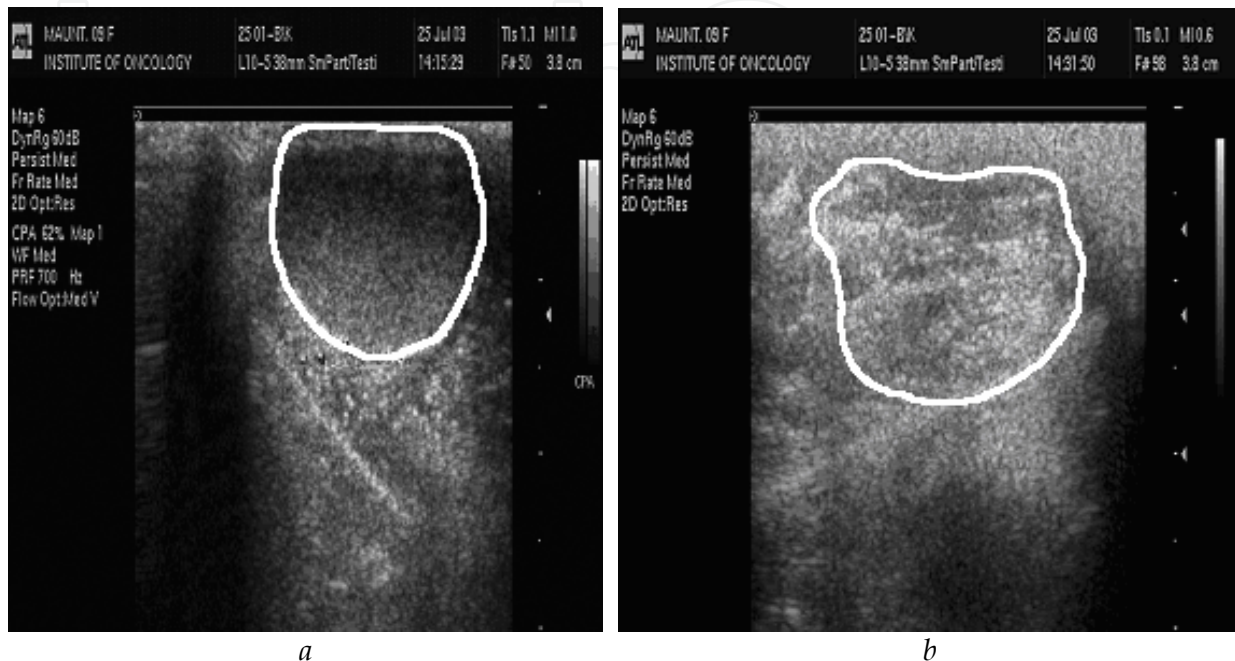


Fig. 8. The sonogram of Guerin carcinoma and tumor heterogeneity parameter  $G$ :  
 a – without EI ( $G = 0.24$ ); b – after 15 min EI ( $G = 0.69$ )

According to the presented data, one may suppose that recorded effects of inhibition or stimulation growth for animal tumors after electromagnetic stimulation may be caused by peculiarity of vascular damages in different experimental tumors.

### 3.2 The effect of spatially inhomogeneous electromagnetic field, local inductive hyperthermia and doxorubicin on nonlinear dynamics of tumor growth for animals with doxorubicin-resistant Guerin's carcinoma

As it is shown in Fig. 9, nonlinear dynamics of the growth for tumor volumes on 10 and 12<sup>th</sup> day after tumor transplantation was identical. Since 14<sup>th</sup> day after transplantation tumor volumes for animals from 4 groups were statistically significant decreased in comparison with the animals of 1, 2 and 3 groups on 88%, 79% and 82% ( $p < 0.05$ ) accordingly in average. The growth kinetics of animal tumors is shown in table 2. The growth kinetics for 3 group had minimal response under the influence of DOXO and EI by ASP generated EF with  $a_E = -0.03$  a.u.;  $a_H = 0.16$  a.u. At the same time the complete resorption were observed on 20<sup>th</sup> day after tumor transplantation for 40% animals from 4 group (DOXO + EI by AAP,  $a_E = 0.89$  a.u. and  $a_H = 0.48$  a.u.). The recurrent tumor growth hadn't been detected for 4 months after the treatment. Obtained results were testified by the study repeated in 4 months.

Our research showed that antitumor effect of DOXO was not depended on the rotation of applicator on horizontal plane relative to tumor. Antitumor effect of DOXO didn't changed significantly under EF after mechanochemical activation of drug before treatment.

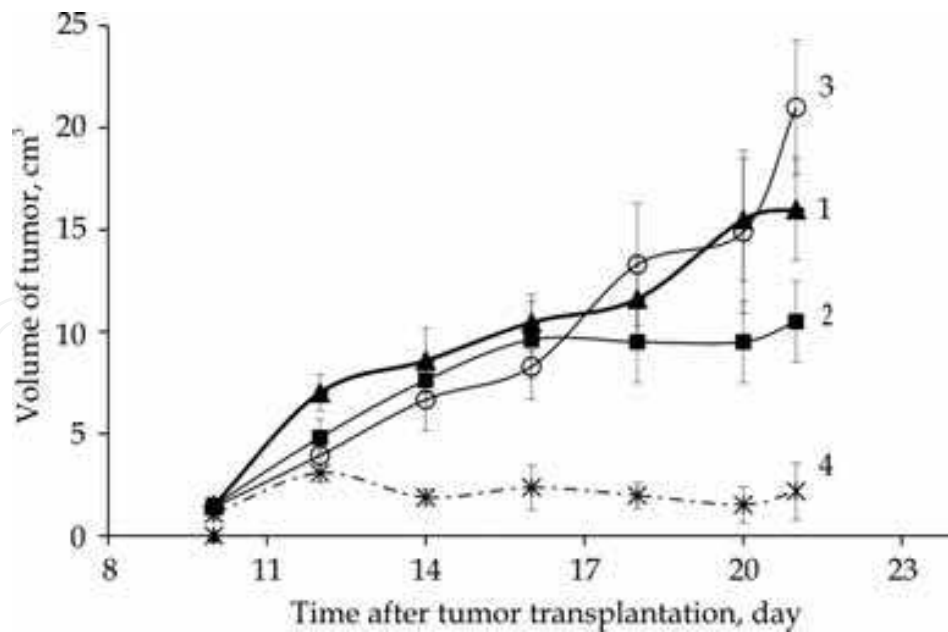


Fig. 9. EI and DOXO-induced changes in nonlinear dynamics of the growth for DOXO-resistant Guerin's carcinoma: 1 - without DOXO and EI (control); 2 - DOXO; 3 - DOXO + EI by ASP; 4 - DOXO + EI by AAP

N	Treatment	Parameters	
		$\varphi, \text{day}^{-1}$	$\kappa$
1	Without DOXO and EI (control)	$0.46 \pm 0.01$	
2	DOXO	$0.42 \pm 0.01$	1.08
3	DOXO + EI by ASP	$0.47 \pm 0.02$	0.97
4	DOXO + EI by AAP	$0.32 \pm 0.02^*$	1.43

\* Statistically significant difference from control group

Table 2. The growth kinetics of animal tumors

### 3.3 Thermography

Thermal patterns of tumor's surface and the panel after EI are presented in Fig. 10. Maximal inhomogeneity of tumor surface and indicative panel that estimated by entropy was

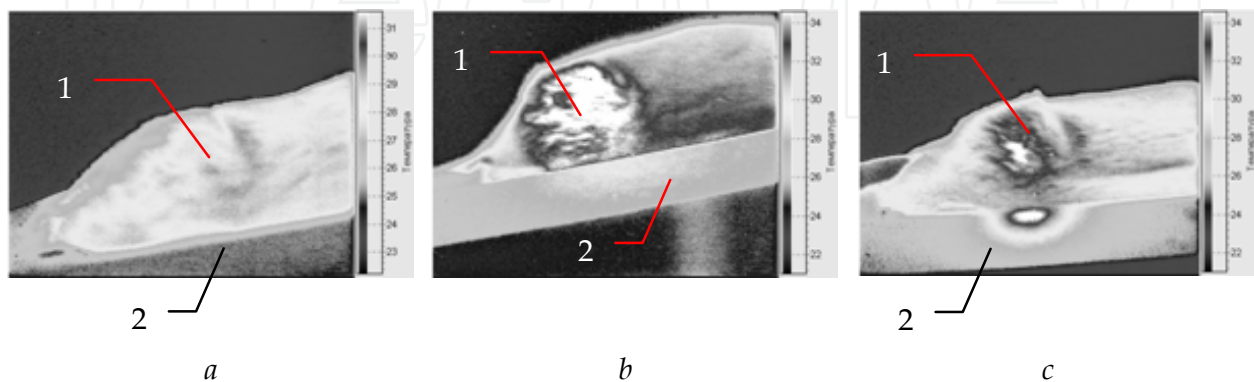


Fig. 10. Change of thermal pattern on tumor surface after transplantation on 15 day (1) and indicative panel (2) after EI; a - without EI (control); b - EI by ASP; c - EI by AAP

obtained for AAP with increased spatial inhomogeneity of EF (Fig. 11). It testifies, that the use of EF with increased spatial inhomogeneity influenced on nonuniform temperature distribution on the surface of animal tumor.

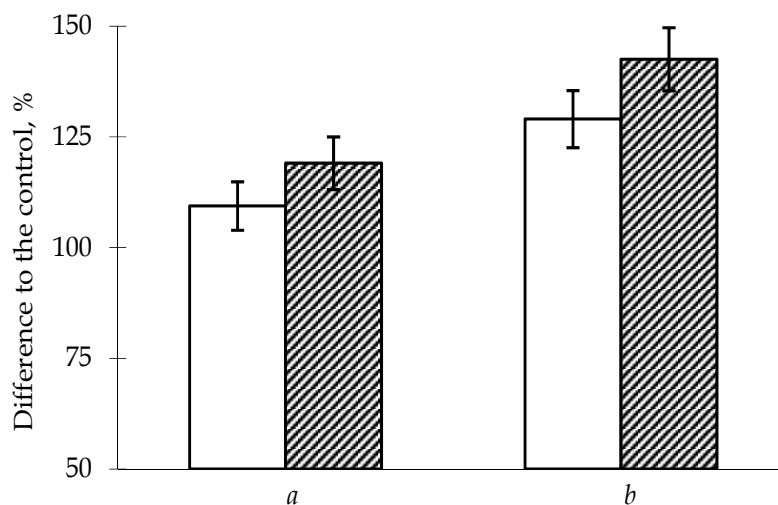


Fig. 11. The inhomogeneity (entropy) of thermal pattern on tumor surface after transplantation on 15 day (a) and indicative panel (b) after EI:  $\square$  - by ASP;  $\text{▨}$  - by AAP. On an axis there is a difference to the control (without EI)

### 3.4 Ultrasonic studies

Typical tumor sonograms on the 15<sup>th</sup> day after the tumor transplantation and 15 minutes of EI are shown in Fig. 12. The computer nonlinear analysis of composite B-mode and steered color Doppler acoustic image demonstrated that heterogeneity  $G$  was decreased by 30% after EI with increased spatial inhomogeneity by AAP. It testifies, that the use of EF with increased spatial inhomogeneity influenced on the vessel dilation in malignant tissues. This is in accordance with aforementioned observations that EI and moderate hyperthermia in a tumor is characterized by the typical change of a tumor's blood flow and increased oxygenation of tumor cells (Song et al., 2005).

## 4. Discussion

### 4.1 The influence of spatially inhomogeneous electromagnetic field and inductive hyperthermia on nonlinear aspects of malignant growth

Our study demonstrated that spatially inhomogeneous electromagnetic fields with asymmetry parameters  $a_E = -0.03$  a.u. and  $a_H = 0.16$  a.u. and local IH in the range physiological hyperthermia cause influence on nonlinear dynamic of the growth of transplanted animal tumor (Orel et al., 2007b). The cancer processes are an example of non-equilibrium, non-linear process. It is predictable locally in the very short-term, but not in the medium- and long-term, as typical of systems exhibiting deterministic chaos (Rubin, 1984). The effects of spatially inhomogeneous EF and local IH in the range physiological hyperthermia warrant increased to create chaos for animal with cancer process. It effects of inducing extremely large and very rapid surges of stochastic endogenous signals in tumor

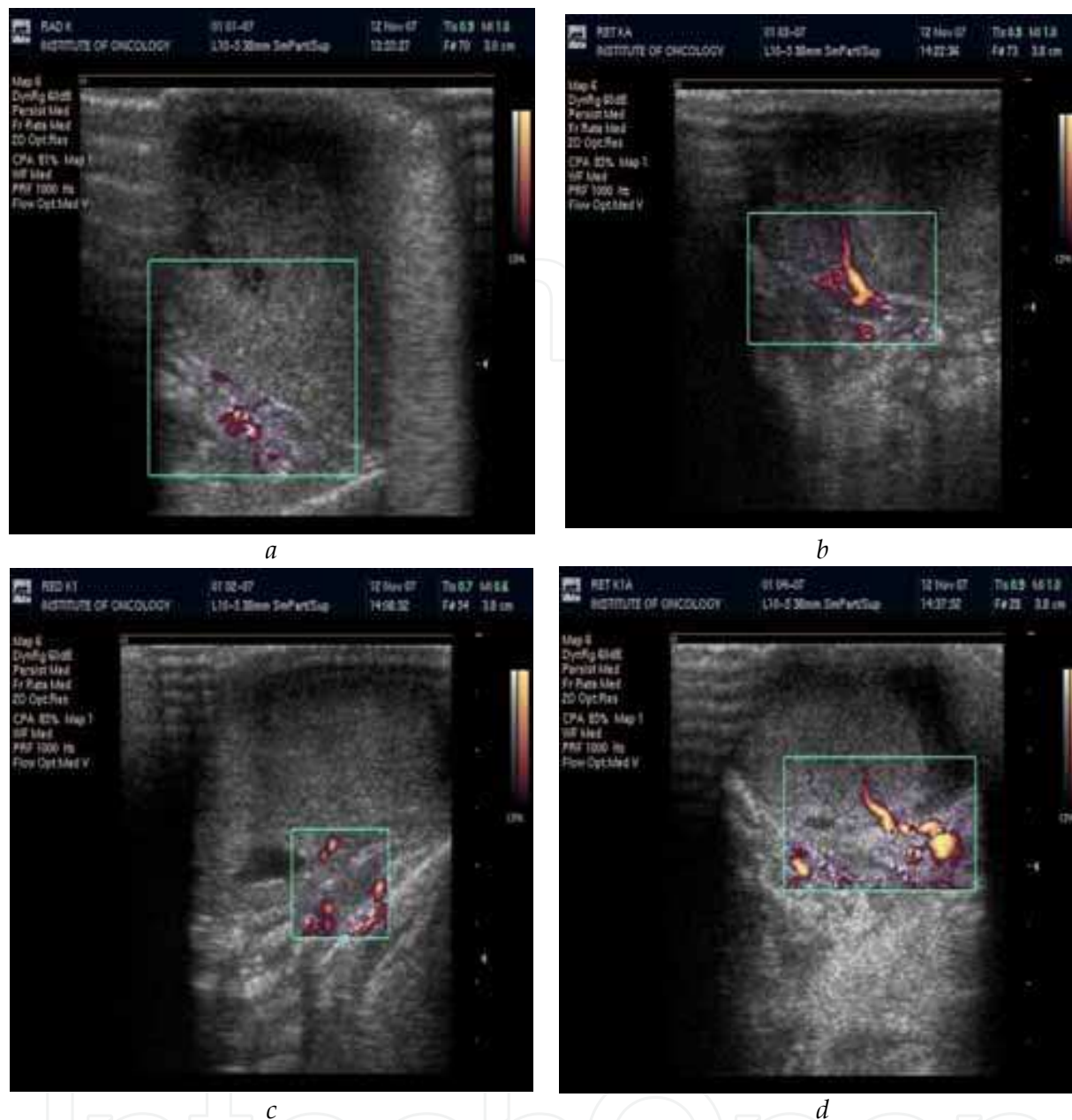


Fig. 12. The change of heterogeneity ( $G$ ) in composite B-mode and steered color Doppler acoustic image of tumor: *a* – without EI (control),  $G = 0.55$ ; *b* – EI by ASP,  $G = 0.56$ ; *c* – without EI (control),  $G = 0.60$ ; *d* – EI by applicator with AAP,  $G = 0.42$

cells. They tend to be quasi (almost but not quite)-periodic, the periodicities are a complex of many periods, and they can swing between different quasi-periodic states. But they are not at all random (Waliszewski et al., 1998; Marino et al., 2000,2009).

Living systems are organized such that they manifest operational features ascribed to hierarchical and heterarchical structures from quantum to organism levels (Dirks, 2008). In mainstream biology that would enable us to understand how EF below the "thermal threshold" could have any effects. That, despite the fact that consistent changes in gene expression and DNA breakages – considered to the 'most solid' evidence – have now been obtained. Some biological effects are indeed associated with EF so weak that the energies in those fields are below the energy of random thermal fluctuations. Molecular signaling in

eukaryotic cells is accomplished by complex and redundant pathways converging on key molecules that are allosterically controlled by a limited number of signaling proteins. p53-signaling pathway is an example of a complicated sequence of signals produced in response to DNA damage. This pattern of signaling may arise from chance occurrences at the origin of life and the necessities imposed on a nanomolar system (Yarosh, 2001; Schneider et al., 2004). Signals from tumor cells look like stochastic processes although their latent mechanism is deterministic. These are the 'butterfly' effects: the molecule of DNA could affect the metabolism in organism (in common with a proverbial butterfly flapping its wings in the Amazon rainforest could affect the weather in London) (Carrubba et al., 2007; Carrubba et al., 2008).

Thereby inhomogeneous EF influence on genetic instability gives rise to the diversity of cancer process. Evidently above mentioned can incarnate of foundation for interpretation different in nonlinear dynamics for transplanted animal tumors.

According to the presented data, one may suppose that recorded effects of inhibition or stimulation growth for animal tumors after spatially inhomogeneous electromagnetic stimulation may be caused by peculiarity of vascular damages in different experimental tumors. These results are important for clinical application of medical technologies because they testify against the use of electromagnetic hyperthermia as a basis for the monotherapy of malignant human tumors and the necessity to facilitate local EI during anticancer neoadjuvant therapy with the use of drugs or magnetic nanoparticles. In general, the application of local electromagnetic hyperthermia in clinical oncology is effective when combined with chemotherapy or radiochemotherapy as shown in (Falk & Issels, 2001).

#### **4.2 An increase of doxorubicin antitumor effect by entropic action of spatially inhomogeneous electromagnetic and heat fields**

The spatially inhomogeneous field is definitely changed by the geometric and mass/structure variance of the tumor itself. The effect of spatially inhomogeneous EF during EI on transformation of radio waves and thermal descriptions in malignant tumors was investigated. It is shown that structure of heat formation in the range physiological hyperthermia on tumor surface depends on the degree of inhomogeneity of EF. In our next experiments revealed entropic action in antitumor effect for DOXO of inhomogeneous electric ( $a_E = 0.89$  a.u.), magnetic fields ( $a_H = 0.48$  a.u.) and temperature in the range physiological hyperthermia during EI.

This action we visualized for other antitumor drug too. The highest antitumor and antimetastatic activity was caused by the combined action of cisplatin and irradiation by spatially inhomogeneous EF and local IH of animals with resistant to cisplatin substrain of Lewis lung carcinoma too (Orel et al., 2009).

The heterogeneous structure of blood vessels in malignant tissue specified by greater specific area of interaction with antitumor drug in comparison with normal tissue. Chaotic signals of inhomogeneous EF can be applied to increase creativity of artificial intelligence, in fluid dynamics of blood to induce turbulence to increase therapeutic effects for antitumor drug, in biochemical processes to drive reactions toward otherwise improbable biochemical compounds, or to raise bond energies above threshold levels without destructive heat. It can be applied to the breaking up of separative attitudes among metastasized cancer cells and aiding in the recovery from cancer (Orel et al., 2004).

What is physicochemical property of spatially inhomogeneous electric, magnetic and temperature fields which influenced on nonlinear dynamics of biological process in the tumor and initiated action as increased antitumor effect for DOXO?

The heterogeneity for tumor structure usually is more variable than for normal tissues. Therefore, we studied influence of EF on transformation of electric, magnetic and thermal fields in heterogeneous (rubber foam + 0.9% NaCl solution) and homogeneous (0.9% NaCl solution) phantoms.

Preliminary research showed that transformation of EF and thermal patterns in phantoms was investigated during EI by spatially inhomogeneous EF (Orel et al., 2008). The change of electric ( $\Delta E$ ) and magnetic ( $\Delta H$ ) component under the influence of phantoms was calculated as follows:

$$\Delta E = E - E_0, \quad (6)$$

$$\Delta H = H - H_0, \quad (7)$$

where  $E$  and  $H$  is electric and magnetic field intensity under phantom,  $E_0$  and  $H_0$  is electric and magnetic field intensity in the air, respectively.

It is shown in Fig. 13 that the structure of heat formation on the surface of phantoms depends on the degree of EF nonuniformity and it is similar to computed in Fig. 5 EF distribution. Relative increase of magnetic field strength  $\Delta H/H_0$  in phantoms after EI by AAP was in 3.5 times greater than by ASP on the average (Table 3). Relative increase of temperature  $\Delta T/T_0$  in phantoms was smaller in 5.4 times after EI by AAP compared to ASP on the average. In rubber foam phantom the ratio  $\Delta T/T_0$  increased in 8.6 times after EI by AAP compared to 0.9% NaCl solution phantom. It testifies stronger transformation of spatially inhomogeneous EF for heterogenous structure of rubber foam phantom than for homogeneous structure of 0.9% NaCl solution phantom. The transformation of inhomogeneous EF to thermal patterns for phantoms was similarly to an effect for animal tumors (see chapter 3.3).

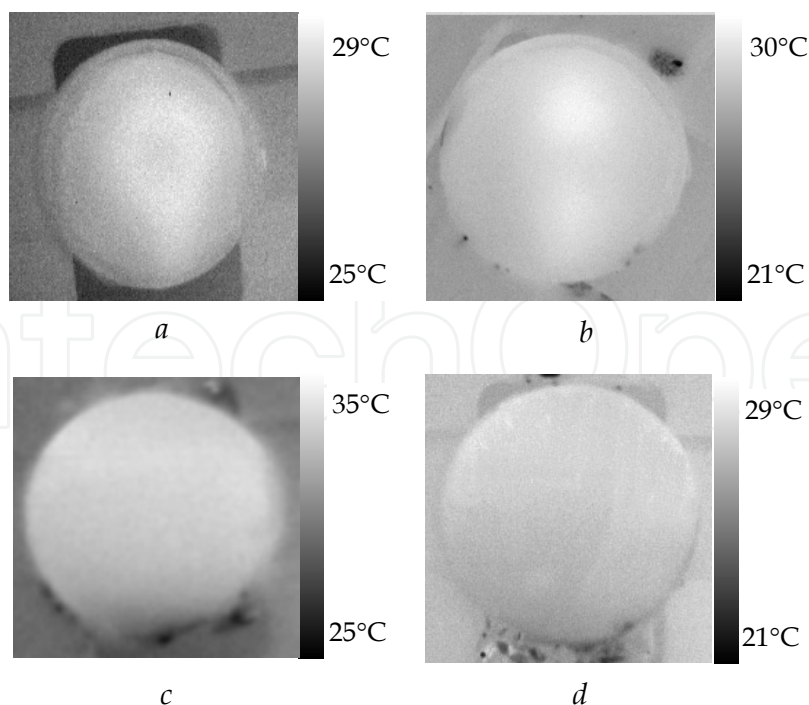


Fig. 13. The change of thermal pattern on phantom surface after electromagnetic irradiation by ASP of foam rubber + 0.9% NaCl solution (a), AAP of foam rubber + 0.9% NaCl solution (b), ASP of 0.9% NaCl solution (c), AAP of 0.9% NaCl solution (d)



Phantom	Applicator	$\Delta E/E_0$ , %	$\Delta H/H_0$ , %	$\Delta T/T_0$ , %
NaCl 0.9% solution	ASP	$47 \pm 3$	$8.0 \pm 1.0$	$0.20 \pm 0.02$
NaCl 0.9% solution	AAP	$19 \pm 3^*$	$20.0 \pm 3.1^*$	$0.10 \pm 0.01$
Foam rubber	ASP	$49 \pm 6$	$7.0 \pm 0.5$	$6.2 \pm 1.0$
Foam rubber	AAP	$28 \pm 4^*$	$31.0 \pm 3.5^*$	$0.7 \pm 0.2^*$

\*  $p < 0.05$  compared to similar parameter of ASP

Table 3. The ratios  $\Delta E/E_0$ ,  $\Delta H/H_0$  and  $\Delta T/T_0$  for phantoms

We studied the transformation of EF and thermal patterns in physiological phantoms – muscular, fatty, liver tissues and packed red blood cells too. The result was similarly to physical phantoms.

Analyzing the above-mentioned phantom researchs, it is possible to mark the problem in our discussion. Is an increase of antitumor effect for drug during treatment under the action of spatially inhomogeneous EF and nonuniform temperature field with temperature peak  $37.9^\circ\text{C}$  accompanied by the tendency of biological system to move toward randomness or disorder that increased thermodynamical entropy in the tumor? As contrasted with our experiments in classic electromagnetic hyperthermia the uniform heat with discrete peaks temperature more  $41^\circ\text{C}$  is basic for cancer therapy (Franckena et al., 2009) that is not enough for essential change of the thermodynamic entropy in the tumor.

To answer on this question we studied the growth dynamics for Guerin carcinoma during treatment by DOXO under influence of inhomogeneous EF and accessory uniform and nonuniform heat in tumor activated by external water heating. Experimental animals were treated by DOXO (Pharmacia & Upjohn) in the dose  $1.5 \text{ mg/kg}$ . The treatment was performed four times by DOXO, EI and external uniform and nonuniform heating by the rubber hot-water bottles from 9 to 15 days after tumor transplantation every other two days. The growth kinetics of Guerin carcinoma was varied for different groups (Table 4). Spatially inhomogeneous EF and nonuniform heat field in the range of physiological hyperthermia was maximally increased antitumor effect of DOXO for transplanted Guerin carcinoma. But temperature in the tumor for this case had a lesser value.

We can suppose that increase of antitumor effect by inhomogeneous EF for drug during treatment of the tumor accompanied by the change of thermodynamical entropy.

Treatment	Temperature in the centre of tumor, $^\circ\text{C}$	Parameters	
		$\varphi$ , $\text{day}^{-1}$	$\kappa$
Control (without DOXO, EI and accessory heat)	36.5	$0.54 \pm 0.06$	1.00
DOXO	36.5	$0.42 \pm 0.02^*$	1.28
DOXO + accessory uniform heat + EI by AAP	41.5	$0.38 \pm 0.01^*$	1.43
DOXO + accessory uniform heat	40	$0.37 \pm 0.01^*$	1.45
DOXO + accessory nonuniform heat	38	$0.36 \pm 0.01^*$	1.50
DOXO + EI by AAP	37.9	$0.35 \pm 0.01^*$	1.53

\* Statistically significant difference from control group

Table 4. The growth kinetics of Guerin carcinoma during 15 days after tumor transplantation

It is well known that EF can initiate electro- and magnetocaloric effects. The electro- and magnetocaloric effects are electro- and magneto-thermodynamic phenomena in which a reversible change in temperature of a suitable material is caused by exposing the material to a changing EF. It was accompanied by changes in transfers from electromagnetic to thermodynamic entropy and enthalpy (Nikiforov, 2007; Crosignani & Tedeschi, 1976). Therefore, we can symbolically include high-frequencies electromagnetic IH in separate class of electro- and magnetocaloric effects.

Described above physicochemical interaction between spatially inhomogeneous electric, magnetic and temperature fields in the phantoms was probably similar to physicochemical interaction in the tumor. They could influence on nonlinear dynamics of biological process. We suppose, that it was interconnection between nonlinear conversion effects of spatial inhomogeneous electric, magnetic fields ( $a_E = 0.89$  a.u.;  $a_H = 0.48$  a.u.) and initiated spatial inhomogeneous temperature field in the heterogeneity tumor structure during propagation of radio waves through malignant tissues. Entropy action is expressed in increase of antitumor effect for DOXO. Alongside located normal tissue toxicity effect was minimal through low level their heterogeneity.

In future we will be able to develop of novel and effective strategies for prevention and treating cancers on the basis of understanding of nonlinear dynamics of adaptive systems associated with tumorigenesis aspects during signaling interaction between cancer cells and the host for complex treatment of patients by whole-body irradiation with local varying spatial inhomogeneous EF.

#### 4.3 Nonlinear model of growth dynamics for transplanted animal tumor during irradiation by spatially inhomogeneous electromagnetic field and inductive hyperthermia

Spatially inhomogeneous EF and initiated it heat manage the formation and disintegration of dissipative structures lying in the basis of self-organization processes in organism at physiological hyperthermia. We applied Waddington's epigenetic landscape model which is a metaphor for how gene regulation modulates development to interpret the changes in thermodynamical parameters (entropy, enthalpy etc.) during nonlinear tumor growth of transplanted animal tumors (Goldberg et al., 2007). The traditional mechanist, pathway-centered explanation assumes that a specific, "instructive signal" i.e., a messenger molecule or external signal of that interacts with its cognate cell surface receptor, tells the cells which particular genes to active in order to establish a new cell phenotype. Essentially, cell distortion triggered the cell to "select" between different preexisting attractor states (Sole, R. et al., 2006). A certain chemical reaction is performed at different temperatures and the reaction rate is determined. The reaction rate ( $k$ ) for a reactant or product in a particular reaction is intuitively defined as how fast a reaction takes place according to the Eyring-Polanyi equation:

$$k = \frac{k_B T}{h} e^{\frac{\Delta S}{R}} e^{-\frac{\Delta H}{RT}}, \quad (8)$$

where:  $k_B$  is Boltzmann's constant,  $h$  is Planck's constant,  $T$  is absolute temperature,  $\Delta S$  is entropy of activation,  $\Delta H$  is enthalpy of activation,  $R$  is gas constant (Polanyi, 1987).

The interaction effect of spatially inhomogeneous EF with heterogenous structure of animal tumors just as described above for the phantoms initiated spatially inhomogeneous thermal

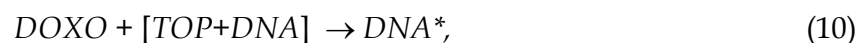
field gradient in malignant tissues in the range physiological hyperthermia. It was accompanied by stochastic changes in transfers from electromagnetic to thermodynamic entropy  $\Delta S$  and enthalpy  $\Delta H$  of activation and, respectively, stochastic changes of the reaction rate that influence on nonlinear (chaotic) aspects in malignant growth (random effect of increase or decrease) for transplanted animal tumors (see chapter 3.1). Spatially inhomogeneous EF with increased asymmetry parameters during treatment of animal tumors by DOXO (Table. 4) accompanied by the change of entropy of activation ( $\Delta S$ ), the reaction rate  $k$  (eq.8) and initiate enzyme catalysis topoisomerase II-mediated DNA damage and free radical formation, absorbing them into double helix of DNA and resulting damage of tumor cells. In this case the number of free radicals increased, in our opinion, as a result of the effect of spin conversion in radical electron pair.

Let us consider kinetic model of tumor growth under the action of DOXO and nonuniform heat field in the range of physiological hyperthermia initiated by spatially heterogeneous EF. Let tumor cells multiplied with the growth factor  $\lambda$ , and DNA of some part of cells loses their ability for replication under the action of DOXO and nonuniform heat field. The appropriate equation can be written as

$$\frac{dx}{dt} = \lambda x - v. \quad (9)$$

where  $x$  is the number of tumor cells in unit volume with capable of replication DNA,  $v$  is the rate of appearing of tumor cells with damaged DNA, which is unable to replicate.

Doxorubicin is known to interact with DNA by intercalation and inhibits the progression of the enzyme topoisomerase II, which unwinds DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication. Schematically this reaction can be written down as:



where  $[TOP+DNA]$  is topoisomerase II complex,  $DNA^*$  is damaged DNA.

Let  $y = C_{DOXO}$  is the concentration of DOXO,  $y(0) = y_0$  - beginning maximal concentration of DOXO,  $y \geq 0$ ;  $u = C_{TOP}$  is the concentration of topoisomerase II,  $u > 0$ . For the open system the concentration of DOXO and TOP in the reaction (10) is described taking into account diffusion:

$$\begin{cases} \frac{\partial y}{\partial t} = -r + D_y \frac{\partial^2 y}{\partial l^2}, \\ \frac{\partial u}{\partial t} = -r + D_u \frac{\partial^2 u}{\partial l^2}, \end{cases} \quad (11)$$

$$\begin{cases} \frac{\partial y}{\partial t} = -r + D_y \frac{\partial^2 y}{\partial l^2}, \\ \frac{\partial u}{\partial t} = -r + D_u \frac{\partial^2 u}{\partial l^2}, \end{cases} \quad (12)$$

where  $r$  is reaction rate,  $D_y$  and  $D_u$  is effective diffusion rate,  $l$  is spatial coordinate.

In accordance with kinetic law of mass action during steady quasistationary regime in the system the rate  $r$  of reaction (10) is expressed as

$$r = ky_u, \quad (13)$$

where  $k$  is the constant of reaction rate (Ederer & Gilles, 2007).

The concentration  $u$  of topoisomerase II is related with the number  $x$  of tumor cells in unit volume:

$$u = ax, \tag{14}$$

where  $a$  is a coefficient.

The rate  $v$  of appearing of tumor cells with damaged DNA determined by the cells with topoisomerase II reacted in (10):

$$v = -\frac{1}{a} \frac{du}{dt}. \tag{15}$$

Putting in (15) the expression for  $\frac{du}{dt}$  from (12) and taking (14) into account, we will get

$$v = \frac{r}{a} - D_x \frac{\partial^2 x}{\partial l^2}. \tag{16}$$

Thus, equations (9) and (11) it is possible to write down as a system:

$$\begin{cases} \frac{dx}{dt} = \lambda x - \frac{r}{a} + D_x \frac{\partial^2 x}{\partial l^2}, \\ \frac{dy}{dt} = -r + D_y \frac{\partial^2 y}{\partial l^2}. \end{cases} \tag{17}$$

The constant of reaction rate  $k$  depends on temperature  $T$  according to Arrhenius equation:

$$k = Ae^{-\frac{E}{RT}}. \tag{18}$$

Taking (13) and (18) into account the system (17) will look like:

$$\begin{cases} \frac{dx}{dt} = \lambda x - Ae^{-\frac{E}{RT}} xy + D_x \frac{\partial^2 x}{\partial l^2}, \\ \frac{dy}{dt} = -aAe^{-\frac{E}{RT}} xy + D_y \frac{\partial^2 y}{\partial l^2}, \end{cases} \tag{19}$$

with initial condition  $y(0) = y_0$  and edge conditions  $x > 0$  and  $y > 0$ .

The system of equations (11) describes the nonuniform thermal effect of the spatially inhomogeneous EF on the growth kinetics of the number of tumor cells under the action of DOXO.

According to the presented data, one may suppose that recorded effects of growth inhibition for DOXO-resistant Guerin's carcinoma after treatment by DOXO and local EI by EF with increased spatial inhomogeneity ( $a_E = 0.89$  a.u.;  $a_H = 0.48$  a.u.) may be connected with the initiation of membrane depolarization due to two steps. Firstly – ionic cyclotron resonance and next – paramagnetic resonance (Liboff AR, 1985; Blanchard & Blackman 1994; Bezrukov & Vodyanoy, 1997), which initiated the antitumor activity of DOXO. Its biochemical mechanisms may be the alteration of the tumor microenvironment via changes in the pH gradient between the extracellular environment and the cell cytoplasm (De Milito & Fais, 2005) and probably EF influency on free radical metabolism of human body (Jin et al., 1998). Thus, we can assert that spatially inhomogeneous EF and local IH initiated in tumor of the reactions with multiple physicochemical properties.

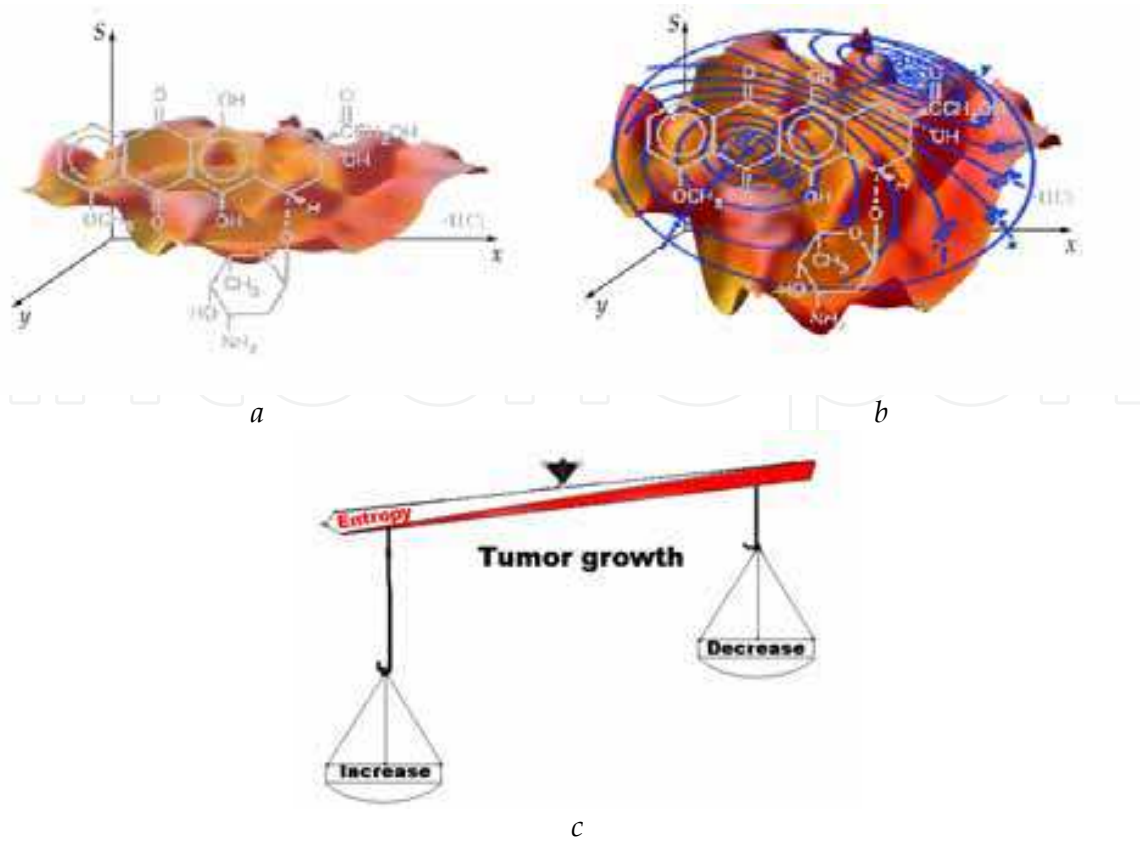


Fig. 14. Spatial distribution of entropy of activation in the tumor during treatment by Doxorubicin hydrochloride  $C_{27}H_{29}NO_{11} \cdot HCl$  and spatial inhomogeneity electromagnetic field with increased asymmetry parameters: *a* – Doxorubicin hydrochloride; *b* – Doxorubicin hydrochloride under the action of spatially inhomogeneous EF and IH; *c* – entropy of activation and tumor growth

Our preclinical and early clinical data suggest that combining superficial and intracellular agents can synergize and leverage single-agent activity. The aforementioned effect of influence of spatially inhomogeneous EF and local IH at physiological temperatures on increase of antitumor activity for drug used in clinical practice during chemotherapy of cancer patients (Nikolov et al., 2008).

## 5. Conclusion

1. EI by spatially inhomogeneous EF and local IH in the range physiological hyperthermia of transplanted animal tumors manifests many of nonlinear (chaotic) aspects in malignant growth.
2. An increase of spatially inhomogeneous EF and local IH in the range physiological hyperthermia increased antitumor effect of DOXO for transplanted DOXO-resistant Guerin's carcinoma and accompanied by the change of thermodynamical entropy.
3. Understanding the chaotic theory for cancer and its interplay may enable similar strategies to be employed in the treatment of cancer by spatially inhomogeneous EF and local IH in the range physiological hyperthermia.

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