Condition evaluation of components of multi-parametric space determining the evolution of carcinogenesis in biological systems

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Abstract: The multi-parametric space 'number of tumor cells – tumor cell volume – glucose level – diffusion saturation level' and its corresponding 3D initial state space components were studied. It was shown that the choice of parameter sets from this space controls the carcinogenesis in biological systems. The model describing interactions of the tumor cells, matrix-metalloproteinases, matrix-degradative enzymes and oxygen was used to simulate the nonlinear multi-scale cancer invasion. The technique based on wandering trajectories analysis was applied to quantify chaotic cancerous attractors in the studied model. Presented are the results of evaluation of conditions in all control parameter planes as well as the modes to inhibit and/or stabilize carcinogenesis.

1. Introduction

This work is a continuation of the study presented in [1] where, based on the performed analysis of the mathematical model describing the tumor development in a biological system, the parameter sets resulting in occurring cancer chaotic attractors have been found in control parameter plane 'number of tumor cells versus diffusion saturation level'. Also it was ascertained a significant influence of the biological system initial state to carcinogenesis and it was illustrated by regions in phase planes of initial conditions. The obtained resluts allowed under definite conditions a controlling and stabilizing unpredictable behavior of metabolic reactions and suppressing carcinogenesis.

It should be noted, that the contradictions found in the recent literature (it is reported, for instance, in [2]) concerning to an influence of glucose level and oxygen concentration on carcinogenesis can be explained *not only* by fact that in those studies the initial state of the biological system was not taking into account, but also that a mutual influence of *all* components of the multy-parametric space of the models studied was not taking into account. In the present work a significant and complex mutual influence of all components of the multy-parametric space 'number of tumor cells – tumor cell volume – glucose level – diffusion saturation level' as well as of the 3D initial state space components on inhibition/amplification of carcinogenesis in biological systems was ascertained. The evolution of conditions conducive to cancer invasion was defined depending on parameters of the multy-parametric space.

2. Mathematical model

Cancer is generally defined as a malignant tissue growth resulting from an uncontrolled division of cells [3]. In the model studied in this work, the tumor development is governed by the inhomogeneous dissipative set of differential equations [4–7, 2]:

$$\dot{n}=0, \tag{1}$$

$$\dot{f}=\alpha\eta(m-f), \tag{2}$$

$$\dot{m}=\beta\quad n+f(\gamma-c)-m, \tag{3}$$

$$\dot{c}=\nu f m-\omega n-\delta\phi c, \tag{4}$$

where n denotes the tumor cell density, f is the matrix–metalloproteinases (MM) concentration, m corresponds to the matrix-degradative enzymes (MDE) concentration, and c denotes the oxygen concentration. Parameters α is a tumor cell volume, β – glucose level, γ – number of tumor cells, δ – diffusion saturation level; η and κ are coefficient that characterise the growth and decay of MM and MDE concentration respectively; υ , ω, φ are parameters that govern growth and decay of the oxygen concentration.

The model (Eqs. 1–4) possesses three chemical equilibria

$$m^{e}_{1,2,3}=f^{e}_{1,2,3}=A+B,-\frac{A+B}{2}\pm\frac{A-B}{2}\sqrt{-3}, \tag{5}$$

$$c^{e}_{1,2,3}=\frac{1}{\delta\phi}\left(\nu\left(f^{e}_{1,2,3}\right)^{2}-\omega n\right), \tag{6}$$

$$A=\sqrt[3]{-\frac{q}{2}+\sqrt{\frac{q^{2}}{4}+\frac{p^{3}}{27}}},\ B=\sqrt[3]{-\frac{q}{2}-\sqrt{\frac{q^{2}}{4}+\frac{p^{3}}{27}}}, \tag{7}$$

$$p=\frac{\delta\phi}{\nu}(1-\gamma-\omega n),\ q=\frac{\delta\phi}{\nu}\beta\quad n. \tag{8}$$

As mentioned in [8] pertaining to the self-organizing chemical systems: as soon as the product is also a part of the same chemical reaction, the system can express unstable behaviour which can be controlled by the reaction parameters. Depending on control parameter values and initial conditions, the considered biological cancerous cell system can also approach different states: a) stationary equilibrium state where any changes are damped; b) stable periodic chemical process or so called ‘chemical clock’ (a limit cycle); c) state of chemical instability with chaotic behaviour of MM, MDE and oxygen concentrations.

3. Numerical results

Cancer chaotic attractors exist within certain parameter ranges of mathematical model (Eqs. 1–4) describing the tumor development in a biological system. In this section multy-parametric space

'number of tumor cells – tumor cell volume – glucose level – diffusion saturation level' is studied. To quantify conditions for carcinogenesis the technique based on the wandering trajectories analysis [9, 10, 1] was applied.

After a discretisation of the multy-parametric space, the governing equations (Eqs. 1–4) are twice solved numerically with two nearby initial conditions. Initial conditions of the nearby trajectories are distinguished by 0.5 percent with ratio to the characteristic vibration amplitudes A_f, A_m, A_c defined as follows

$$A_f = \frac{1}{2}\left| \max_{t_1 \le t \le T} f(t) - \min_{t_1 \le t \le T} f(t) \right| , \tag{5}$$

$$A_m = \frac{1}{2}\left| \max_{t_1 \le t \le T} m(t) - \min_{t_1 \le t \le T} m(t) \right| , \tag{6}$$

$$A_c = \frac{1}{2}\left| \max_{t_1 \le t \le T} c(t) - \min_{t_1 \le t \le T} c(t) \right| , \tag{7}$$

e.g. the starting points of these trajectories are in the three-dimensional parallelepiped

$$\left| f(t_0) - \tilde{f}(t_0) \right| < 0.005\, A_f \tag{8}$$

$$\left| m(t_0) - \tilde{m}(t_0) \right| < 0.005\, A_m \tag{9}$$

$$\left| c(t_0) - \tilde{c}(t_0) \right| < 0.005\, A_c . \tag{10}$$

Characteristic vibration amplitudes A_f, A_m, A_c are calculated for all nodal points of the multy-parametric space simultaneously with integration of the governing equations (Eqs. 1–4). After integration of the governing equations (Eqs. 1–4), the condition

$$\exists t^* \in [t_1, T]: \quad \{ (\left| f(t^*) - \tilde{f}(t^*) \right| > \alpha A_f) \vee (\left| m(t^*) - \tilde{m}(t^*) \right| > \alpha A_m) \vee (\left| c(t^*) - \tilde{c}(t^*) \right| > \alpha A_c) \} \tag{11}$$

was verified. Here T is the time period for the simulation; $[t_0, t_1]$ is the time interval, where transient processes are damped. The manifold of the nodal points of the multy-parametric space, for which the inequality (Eq. 11) is satisfied, resulting in setting up the regions of chaos.

An evolution of the chaotic regions in the control parameter plane 'tumor cell volume vs glucose level' ($\beta\kappa n$, $\alpha\eta$), ($0 \le \beta\kappa n \le 300$, $0 \le \alpha\eta \le 10$), depending on magnitude of diffusion saturation level $\delta\varphi$=0.5, $\delta\varphi$=1.0 and $\delta\varphi$=2.0 for the model (Eqs. 1–4) is observed in Fig. 1 (a), (b), (c). Other parameters n=50, γ= 100, η=50, κ=1, υ=0.5, ω=0.57, φ=0.025 are fixed and the initial conditions are taken $f(0)$=5.0; $m(0)$=5.0; $c(0)$=10.0.

On the increase of the diffusion saturation level, the regions of conditions conducive to cancer invasion are expanding. For the parameter ranges considered chaotic cancer attractors are generated

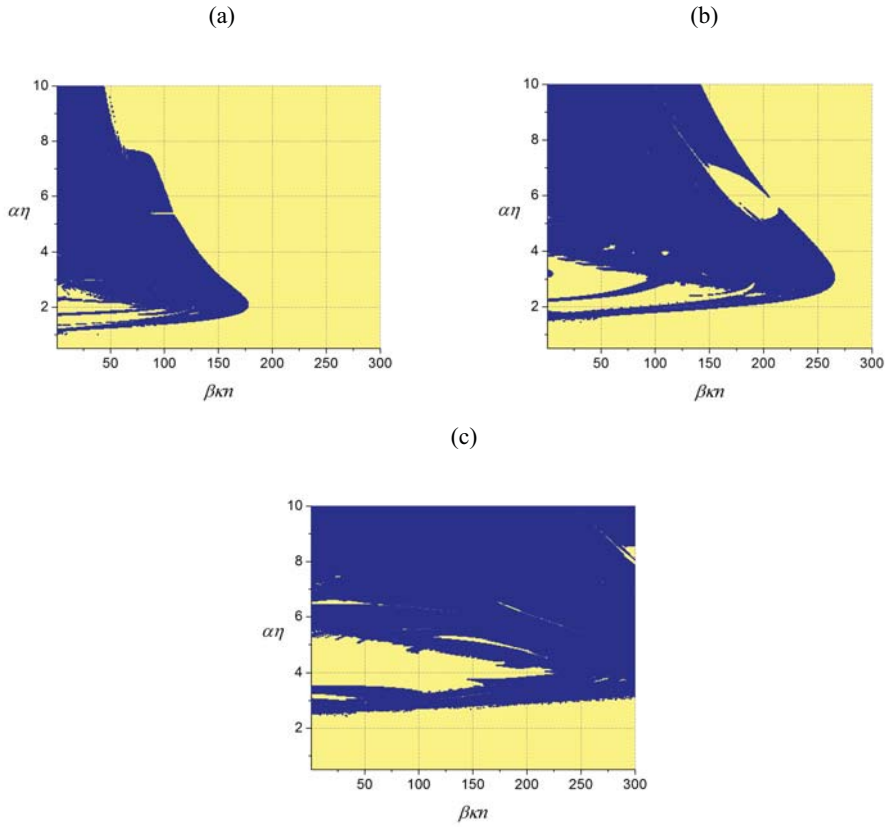

Figure 1. Control parameter plane ($\beta\kappa n$, $\alpha\eta$) – 'tumor cell volume vs glucose level': evolution of conditions conducive to cancer invasion with increasing magnitude of diffusion saturation level (a) $\delta\varphi$=0.5; (b) $\delta\varphi$=1.0; (c) $\delta\varphi$=2.0.

for glucose levels $\beta\kappa n<\beta_{cr}\kappa n$, where $\beta_{cr}\kappa n$=175.0 at diffusion saturation level $\delta\varphi$=0.5 (Fig. 1, (a)), $\beta_{cr}\kappa n$=270.0 at $\delta\varphi$=1.0 (Fig. 1, (b)) and for any glucose level at $\delta\varphi$=2.0 (Fig. 1, (c)). It should be noted, all obtained regions in the parametric space have complex structure and substantially depend on other parameters of the model (Eqs. 1–4) including initial conditions.

An evolution of the chaotic regions in control parameter plane 'number of tumor cells vs tumor cell volume' ($\alpha\eta$, γ), ($0\leq\alpha\eta\leq10$, $0\leq\gamma\leq200$), depending on glucose level $\beta\kappa n$=2.5, $\beta\kappa n$=250.0, and $\beta\kappa n$=500.0 for the model (Eqs. 1–4) is observed in Fig. 2 (a), (b), (c). Other parameters $\delta\varphi$=1.2, n=50, δ=48.0, η=50, κ=1, υ=0.5, ω=0.57, φ=0.025 are fixed and the initial conditions are taken $f(0)$=5.0; $m(0)$=5.0; $c(0)$=10.0.

Fig. 2 demonstrates, that for the parameter ranges considered, increase in glucose level substantially decreases a risk of cancer invasion in the biological system (see Fig. 2 (c): no chaotic

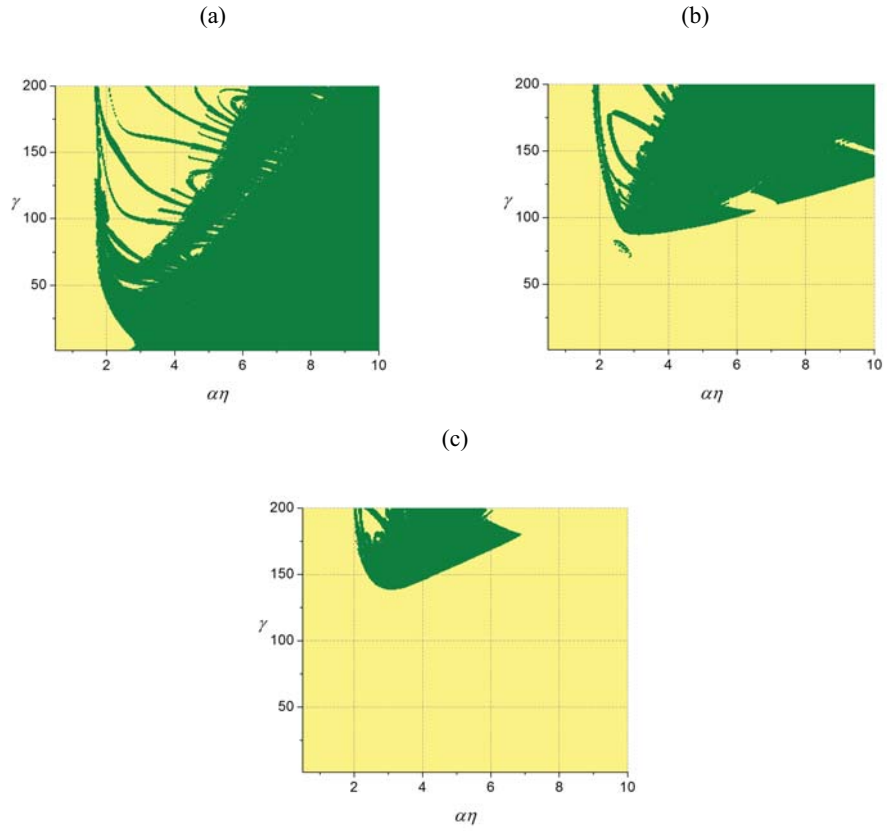

Figure 2. Control parameter plane ($\alpha\eta$, γ) – 'number of tumor cells vs tumor cell volume': evolution of conditions conducive to cancer invasion with increasing glucose level: (a) $\beta\kappa n$=2.5; (b) $\beta\kappa n$=250.0; (c) $\beta\kappa n$=500.0.

cancer attractors when γ<140.0 $\vee$ $\alpha\eta$<2.0 $\vee$ $\alpha\eta$>7.0 at $\beta\kappa n$=500.0). It should be noted, depending on accepted parameters, increase in the diffusion saturation level can lead to both suppression and generation of conditions conducive to cancer invasion (figures and diagrams, confirming this statement, are not presented here due to a brief content of this paper).

We can observe also, in the parametric space 'number of tumor cells vs tumor cell volume' there is some critical threshold $\alpha=\alpha_{cr}$, that chaotic cancerous attractors exist only for $\alpha>\alpha_{cr}$ (see Fig. 2 (a), (b), (c): α_{cr} = 1.9). It is clear, α_{cr} depends on other parametes of the model (Eqs. 1–4) and α_{cr} increases for bigger magnitudes of diffusion saturation level.

An evolution of the chaotic regions in the control parameter plane 'tumor cell volume vs diffusion saturation level' ($\delta\varphi$, $\alpha\eta$), ($0\leq\delta\varphi\leq3.0$, $0\leq\alpha\eta\leq10.0$), depending on number of tumor cells

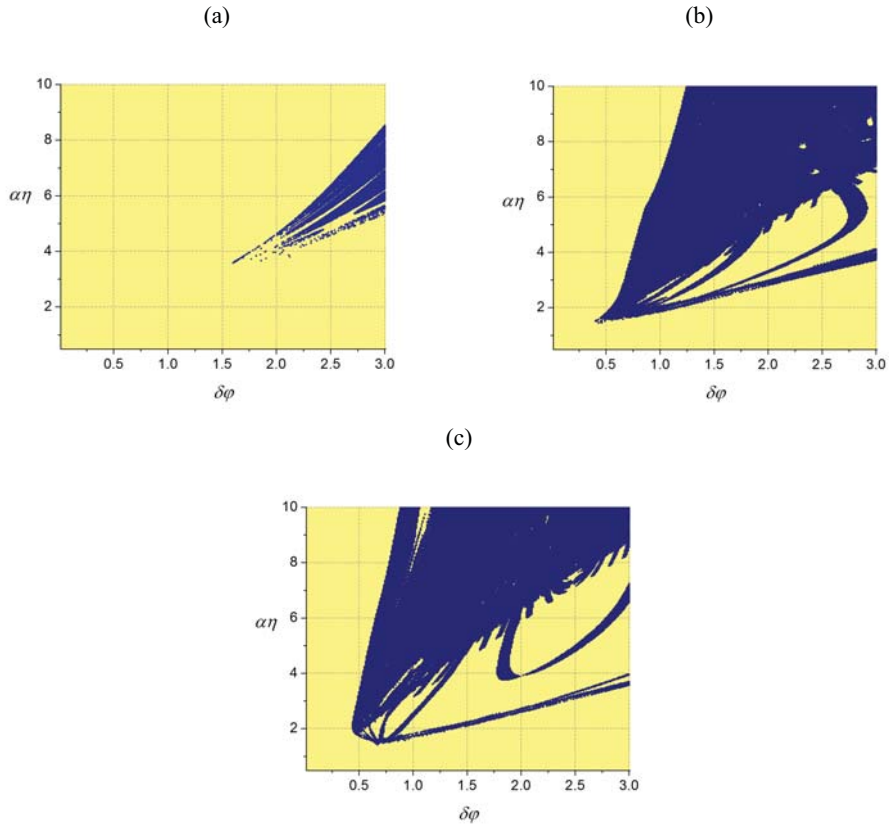

Figure 3. Control parameter plane ($\delta\varphi$, $\alpha\eta$) – 'tumor cell volume vs diffusion saturation level': evolution of conditions conducive to cancer invasion with increasing number of tumor cells: (a) γ=70.0; (b) γ=150.0; (c) γ=200.0.

γ=70.0, γ=150.0 and γ=200.0 for the model (Eqs. 1–4) is observed in Figure 3 (a), (b), (c). Other parameters $\beta\kappa n$= 300.0, n=50, β=6.0, η=50, κ=1, υ=0.5, ω=0.57, φ=0.025 are fixed and the initial conditions are taken $f(0)$=5.0; $m(0)$=5.0; $c(0)$=10.0.

The study of the parametric space 'tumor cell volume vs diffusion saturation level' confirms again a substantial mutual influence of all parameters of the model (Eqs. 1–4) to cancer invasion. Indeed, at comparatively low glucose levels (for instance, $\beta\kappa n$=2.5) regions of chaotic cancerous attractors are suppressed with an increase of number of tumor cells (figures and diagrams, confirming this statement, are not presented here due to a brief content of this paper) while for higher glucose levels (for instance, $\beta\kappa n$=300.0) cancer invasion risk strengthens on the increase of number of tumor cells (see Fig. 3 (a), (b), (c)). Generally, at fixed number of tumor cells the increase in glucose level

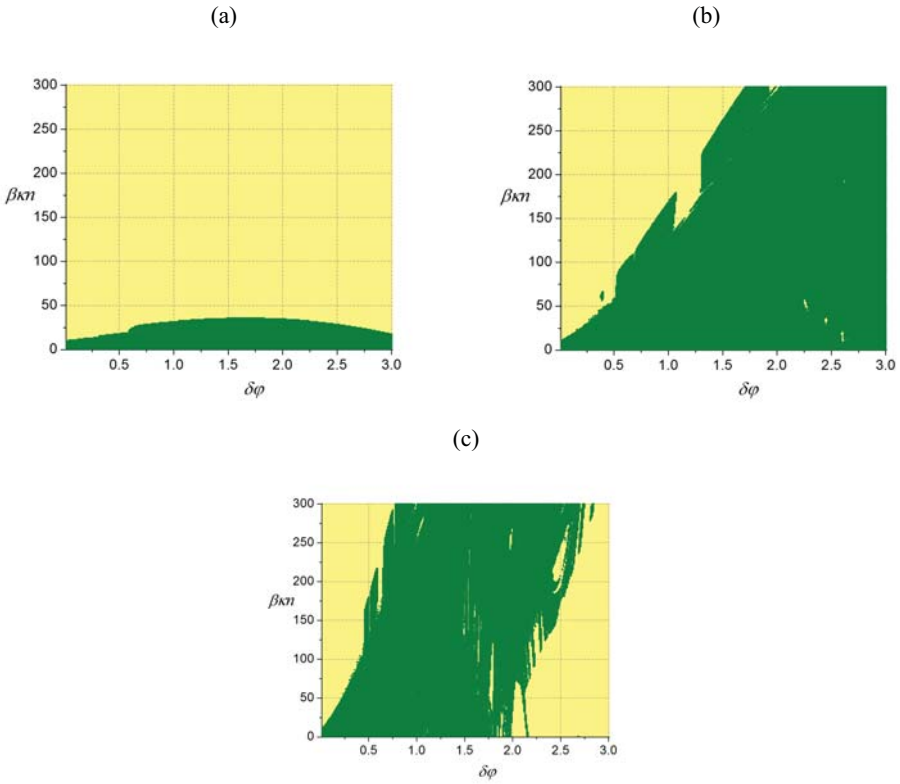

Figure 4. Control parameter plane ($\delta\varphi$, $\beta\kappa n$) – 'glucose level vs diffusion saturation level': evolution of conditions conducive to cancer invasion with increasing number of tumor cells: (a) γ=20.0; (b) γ=100.0; (c) γ=200.0.

has a suppressing effect on carcinogenesis (figures and diagrams, confirming this statement, are not presented here due to a brief content of this paper).

An evolution of the chaotic regions in the control parameter plane 'glucose level vs diffusion saturation level' ($\delta\varphi$, $\beta\kappa n$), ($0\le\delta\varphi\le3.0$, $0\le\beta\kappa n\le300$), depending on number of tumor cells γ=20.0, γ=100.0 and γ=200.0 for the model (Eqs. 1–4) is observed in Figure 4 (a), (b), (c). Other parameters $\alpha\eta$= 8.0, n=50, α=0.16, η=50, κ=1, υ=0.5, ω=0.57, φ=0.025 are fixed and the initial conditions are taken $f(0)$=5.0; $m(0)$=5.0; $c(0)$=10.0.

For the considered planes 'glucose level vs diffusion saturation level' as sections of the multy-parametric space of the model (Eqs. 1–4) both for comparatively small and for comparatively large tumor cell volumes, a consistent pattern is observed: with an increase in the number of tumor cells, the regions of chaotic cancerous attractors in this plane ($\delta\varphi$, $\beta\kappa n$) first increase (see transition from

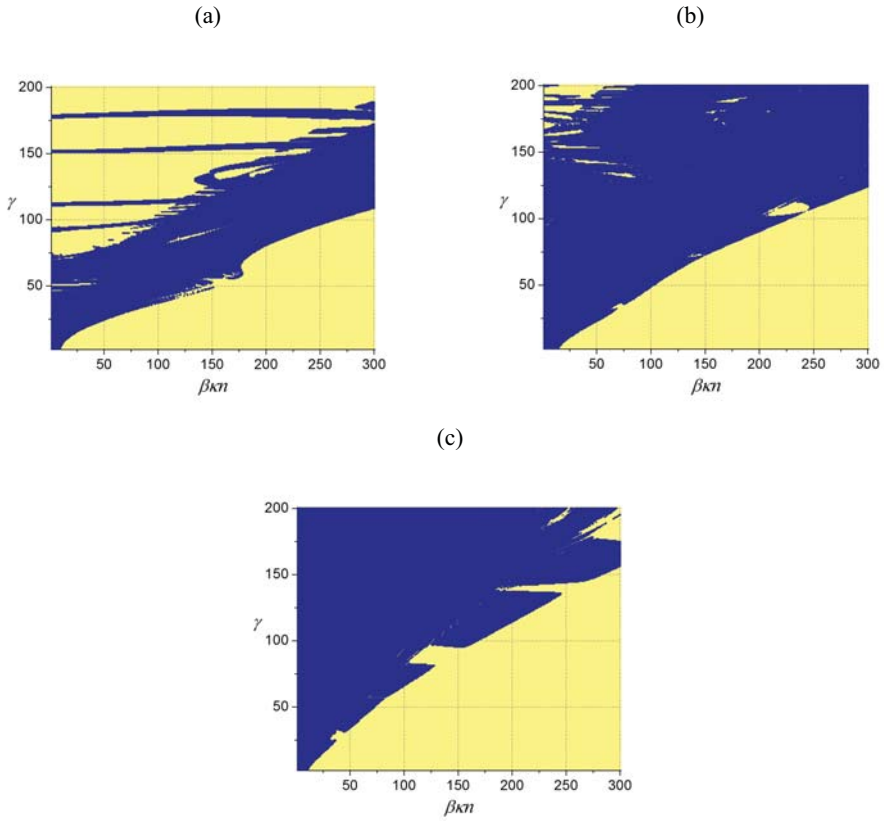

Figure 5. Control parameter plane ($\beta\kappa n$, γ) – 'number of tumor cells vs glucose level': evolution of conditions conducive to cancer invasion with increasing tumor cell volume: (a) $\alpha\eta$=3.0; (b) $\alpha\eta$=5.0; (c) $\alpha\eta$=8.0.

Fig. 4 (a) to Fig. 4 (b)) and then decrease (see transition from Fig. 4 (b) to Fig. 4 (c)). In most of the previous cases, an increase in glucose level led to the suppression of regions of chaotic cancerous attractors. However, in the parametric plane ($\delta\varphi$, $\beta\kappa n$) there are regimes (for instance, at $\alpha\eta$= 3.0, γ= 100.0; $\alpha\eta$= 5.0, γ= 100.0, etc.) corresponding to absence of conditions for carcinogenesis at definite values of glucose level, while a cancer invasion appears when glucose level increases (figures and diagrams, confirming this statement, are not presented here due to a brief content of this paper).

An evolution of the chaotic regions in the control parameter plane 'number of tumor cells vs glucose level' ($\beta\kappa n$, γ), ($0\leq\beta\kappa n\leq300$, $0\leq\gamma\leq200$), depending on tumor cell volume $\alpha\eta$=3.0, $\alpha\eta$=5.0 and $\alpha\eta$=8.0 for the model (Eqs. 1–4) is observed in Figure 5 (a), (b), (c). Other parameters $\delta\varphi$=1.0, n=50,

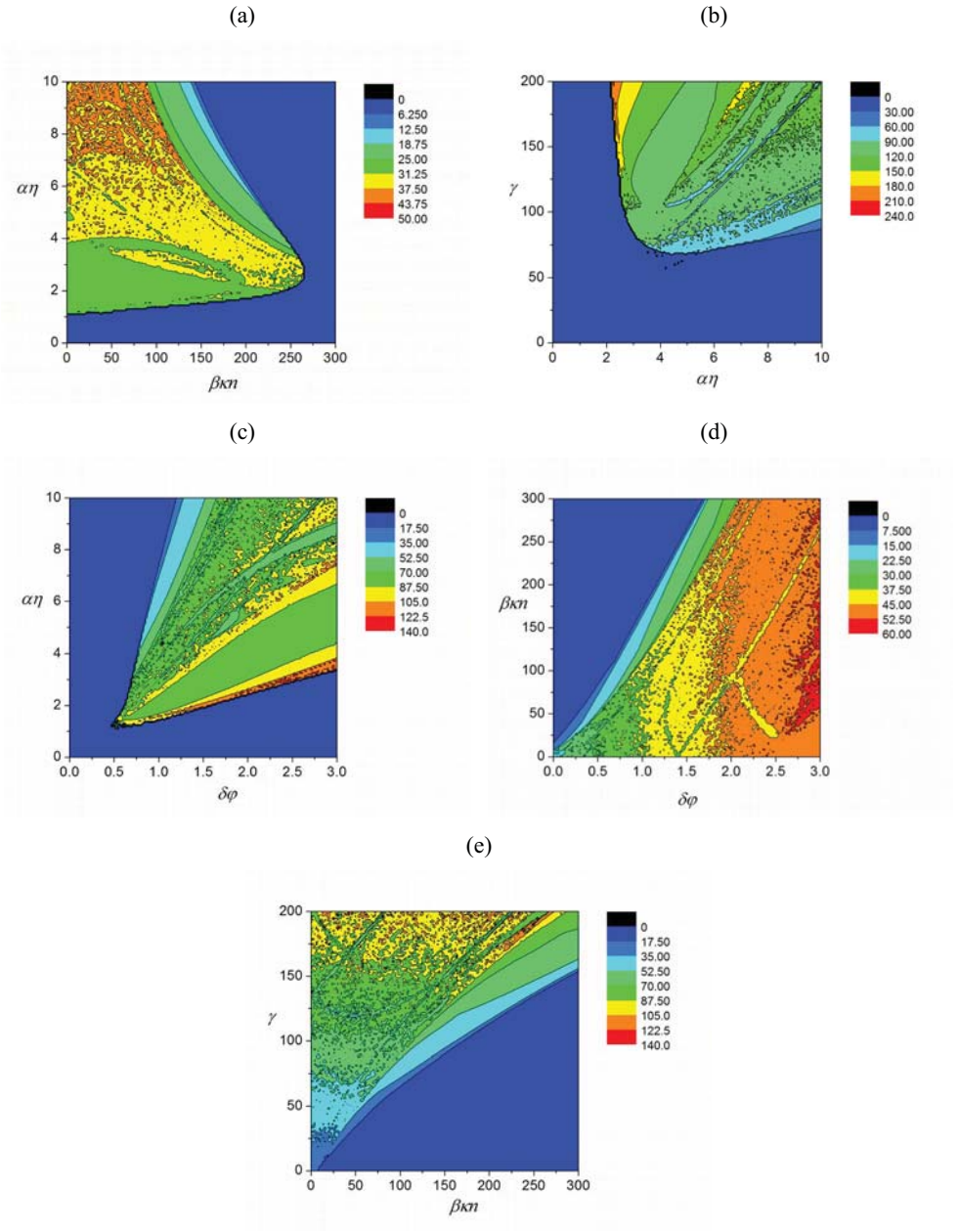

Figure 6. Amplitude level contours of (a) MM concentration in ($\beta\kappa n$, $\alpha\eta$) control parameter plane at γ=100.0, $\delta\varphi$=1.0; (b) MDE concentration in ($\alpha\eta$, γ) plane at $\beta\kappa n$=250.0, $\delta\varphi$=2.0; (c) oxygen concentration in ($\delta\varphi$, $\alpha\eta$) plane at $\beta\kappa n$=300.0, γ=150.0; (d) MM concentration in ($\delta\varphi$, $\beta\kappa n$) plane at $\alpha\eta$=8.0, γ=100.0; (e) MDE concentration in ($\beta\kappa n$, γ) plane at $\alpha\eta$=8.0, $\delta\varphi$=1.0.

δ=40.0, η=50, κ=1, υ=0.5, ω=0.57, φ=0.025 are fixed and the initial conditions are taken $f(0)$=5.0; $m(0)$=5.0; $c(0)$=10.0.

Under conditions considered for comparatively low diffusion saturation levels, for instance $\delta\varphi$= 0.5, chaotic cancerous attractors regions are suppressed with increasing tumor cell volumes and vice versa: for more higher diffusion saturation levels, for instance $\delta\varphi$= 2.0, with increasing tumor cell volumes ($\alpha\eta$= 3.0, $\alpha\eta$= 5.0, $\alpha\eta$= 8.0) the cancer invasion is increased (figures and diagrams for both cases of diffusion saturation levels $\delta\varphi$= 0.5 and $\delta\varphi$= 2.0, confirming this statement, are not presented here due to a brief content of this paper). In Fig. 5 (b), (c) we can observe: there is some glucose level threshold β_{cr}= $\beta_{cr}(\gamma)$ such that no carcinogenesis while $\beta>\beta_{cr}(\gamma)$. So, passing this threshold in the direction of increase, the definite glucose level completely suppresses carcinogenesis. It should be noted, Fig. 5 (a), where chaotic cancer attractors regions have an inclined stripe form, demonstrates another scenario. Thus, at $\alpha\eta$= 3.0, $\delta\varphi$=1.0 (Fig. 5 (a)) (or in other cases, for instance, ($\alpha\eta$= 3.0, $\delta\varphi$=2.0) or ($\alpha\eta$= 5.0, $\delta\varphi$=2.0) etc.) in the parametric plane ($\beta\kappa n$, γ) with increasing of glucose level the state 'no conditions for carcinogenesis' passes to the state 'cancer invasion' and then again passes to the state 'no conditions for carcinogenesis'. That is, depending on other parameters of the model (Eqs. 1–4), increasing in glucose level can both suppress and generate carcinogenesis.

For all studied control parameter planes the corresponding amplitude level contours of matrix-metalloproteinases (MM), matrix–degradative enzymes (MDE) and oxygen concentrations have been obtained and juxtaposed with them. In all cases the carcinogenesis is accompanied by significant increase in chemical oscillation amplitudes of the MM, MDE and oxygen concentrations. Some amplitude level contours of these characteristics are reported in Fig. 6.

Amplitude level contours of matrix-metalloproteinases (MM) concentrations are presented in Fig. 6, cases (a) and (d). Case (a): control parameter plane ($\beta\kappa n$, $\alpha\eta$) 'tumor cell volume vs glucose level' at γ= 100.0, $\delta\varphi$= 1.0 in accordance with Fig. 1 (b) with the same other fixed parameters as for the case of Fig. (b). Case (d): control parameter plane ($\delta\varphi$, $\beta\kappa n$) 'glucose level vs diffusion saturation level' at $\alpha\eta$=8.0, γ=100.0 in accordance with Fig. 4 (b) with the same other fixed parameters as for the case of Fig. 4 (b).

Amplitude level contours of matrix–degradative enzymes (MDE) concentrations are presented in Fig. 6, cases (b) and (e). Case (b): control parameter plane ($\alpha\eta$, γ) 'number of tumor cells vs tumor cell volume' at $\beta\kappa n$= 250.0, $\delta\varphi$= 2.0 in accordance with Fig. 2 (b) with the same other fixed parameters as for the case of Fig. 2 (b). Case (e): control parameter plane ($\beta\kappa n$, γ) 'number of tumor cells vs glucose level' at $\alpha\eta$=8.0, $\delta\varphi$=1.0 in accordance with Fig. 5 (c) with the same other fixed parameters as for the case of Fig. 5 (c).

And finally, amplitude level contours of oxygen concentration is presented in Fig. 6 (c) in control parameter plane ($\delta\varphi$, $\alpha\eta$) 'tumor cell volume vs diffusion saturation level' at $\beta\kappa n$=300.0, γ=150.0 in accordance with Fig. 3 (b) with the same other fixed parameters as for the case of Fig. 3 (b).

Figure 6 demonstrates, that in all cases the carcinogenesis is accompanied by a significant increase in chemical oscillations amplitudes of MM, MDE and oxygen concentrations.

4. Conclusions

In this study it was demonstrated a significant and complex mutual influence of all components of the multy-parametric space 'number of tumor cells – tumor cell volume – glucose level – diffusion saturation level' as well as of the 3D initial state space components on inhibition/amplification of carcinogenesis in biological systems. A nonlinear multi-scale diffusion cancer invasion model that describes the interactions of the tumor cells, matrix-metalloproteinases, matrix-degradative enzymes and oxygen was used for simulation. To quantify chaotic cancer attractors the technique based on the wandering trajectories analysis was applied. Conditions conducive to cancer invasion were defined depending on parameters of the multy-parametric space. The numerous figures presented describe the evolution of these conditions in the process when some parameters of the multy-parametric space were changed. Amplitude level contours of matrix–metalloproteinases, matrix–degradative enzymes and oxygen concentrations have been obtained and juxtaposed with the corresponding parametric planes. In all cases the carcinogenesis is accompanied by significant increase in chemical oscillation amplitudes of matrix–metalloproteinases, matrix–degradative enzymes and oxygen concentrations. The results obtained allow evaluation of conditions in all control parameter planes as well as the modes to inhibit and/or stabilize carcinogenesis.

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