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MULTI-PARAMETRIC CONTROLLING CANCER CELL INVASION IN BIOLOGICAL SYSTEMS WITH MEMORY OF STATES

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Abstract: A model for non-linear multi-scale diffusion cancer invasion was generalized for the case of biological systems with response delay. Modelling was based on the Masing–Bouc-Wen's framework with extra state variables (internal variables) added to simulate the memory of states. Chaotic attractors were quantified based on the wandering trajectories analysis. Comparison of the conditions leading to cancer invasion for the generalized model with and without memory is presented.

Keywords: biological system with memory of states; tumor growth; carcinogenesis; chaotic attractors; response delay

MSC2020: 34C28; 34H10; 34C55; 34A34; 34A36; 92-10.

1 Introduction

This work is the continuation of the earlier studies [1–2] in which the conditions controlling cancer invasion in a biological system were defined depending on parameters of the multi-parametric space as well as it was ascertained a significant influence of the biological system initial state to carcinogenesis. Due to presence of memory of states in these systems, the real biological systems exhibit their response to external perturbations with a certain delay. The biological system remembers in what initial state it was before the changes in functioning conditions and its transition to a new state depends on the pre-history of its behavior resulting in hysteresis (delayed response). The purpose of this study is to model the memory of states in the biological system and to evaluate how hysteretic properties define conditions leading to cancer invasion.

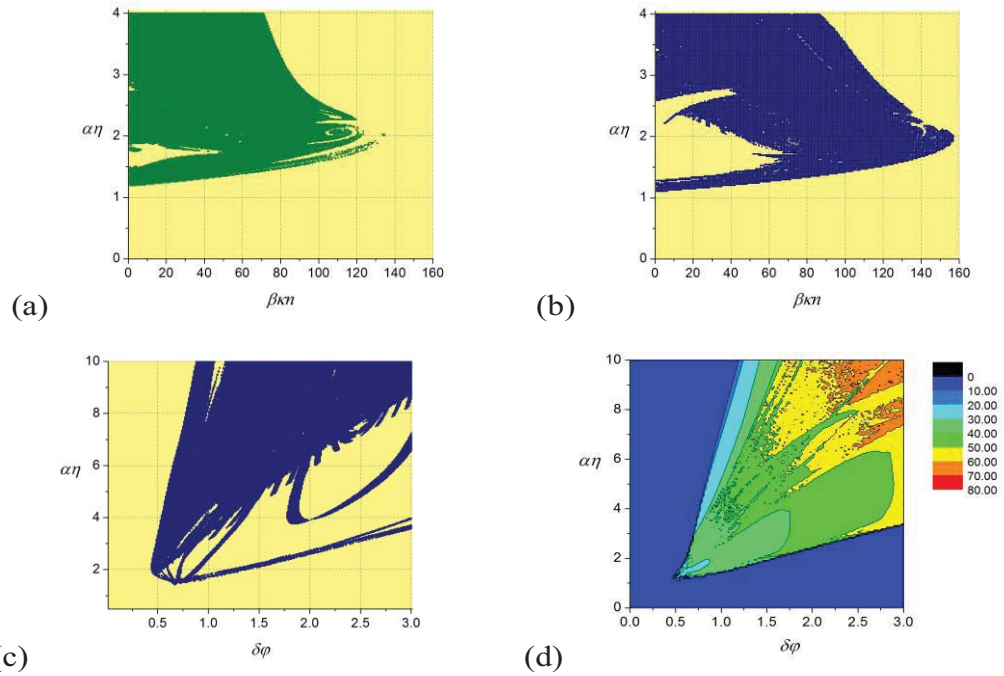

Fig. 1. Conditions leading to cancer invasion in the biological system with the memory of states (1)-(7): (a),(b) in control parameter plane ($\beta\kappa n$, $\alpha\eta$) – 'tumor cell volume vs glucose level' with values of the memorization parameters (a) h_f=0, h_m=0, h_c =0 – case of 'no memory'; and (b) h_f=0.9, h_m=0.9, h_c=0.9 – case 'with memory'; (c) in control parameter plane ($\delta\varphi$, $\alpha\eta$) – 'tumor cell volume vs diffusion saturation level' with corresponding (d) amplitude level contours of MM concentration.

2 Mathematical Model and Simulation Results

The generalized non-linear multi-scale diffusion cancer invasion model with additional state variables is governed by the inhomogeneous dissipative set of differential equations with discontinuities:

$$\dot{n} = 0, \tag{1}$$
$$\dot{f} = \alpha\eta(m - f) + h_f z_f, \tag{2}$$
$$\dot{z}_f = \left[A_f - \left(\gamma_f + \beta_f sgn(\dot{f})sgn(z_f)\right)|z_f|^{n_f}\right]\dot{f}, \tag{3}$$
$$\dot{m} = \beta\kappa n + f(\gamma - c) - m + h_m z_m, \tag{4}$$
$$\dot{z}_m = \left[A_m - \left(\gamma_m + \beta_m sgn(\dot{m})sgn(z_m)\right)|z_m|^{n_m}\right]\dot{m}, \tag{5}$$
$$\dot{c} = \upsilon fm - \omega n - \delta\phi c + h_c z_c, \tag{6}$$
$$\dot{z}_c = \left[A_c - \left(\gamma_c + \beta_c sgn(\dot{c})sgn(z_c)\right)|z_c|^{n_c}\right]\dot{c}. \tag{7}$$

The variables are defined as follows: n – tumor cell density; f – matrix–metalloproteinases (MM) concentration; m – matrix-degradative enzymes (MDE) concentration; c – oxygen concentration; z_f, z_m, z_c present the hysteretic part of the system considered. The fitting parameters are defined as follows: α – tumor cell volume; β – glucose level; γ – number of tumor cells; δ – diffusion saturation level; η and κ are coefficients describing a growth and decay of MM and MDE concentration, respectively; υ , ω, φ govern growth and decay of the oxygen concentration. The parameters (A_f, β_f, n_f), (A_m, β_m, n_m), (A_c, β_c, n_c)$\in R^+$ and γ_f , γ_m , $\gamma_c \in R$ govern the shape of the hysteresis loops. The memorization parameters h_f, h_m, h_c characterise a hysteresis contribution to the system considered.

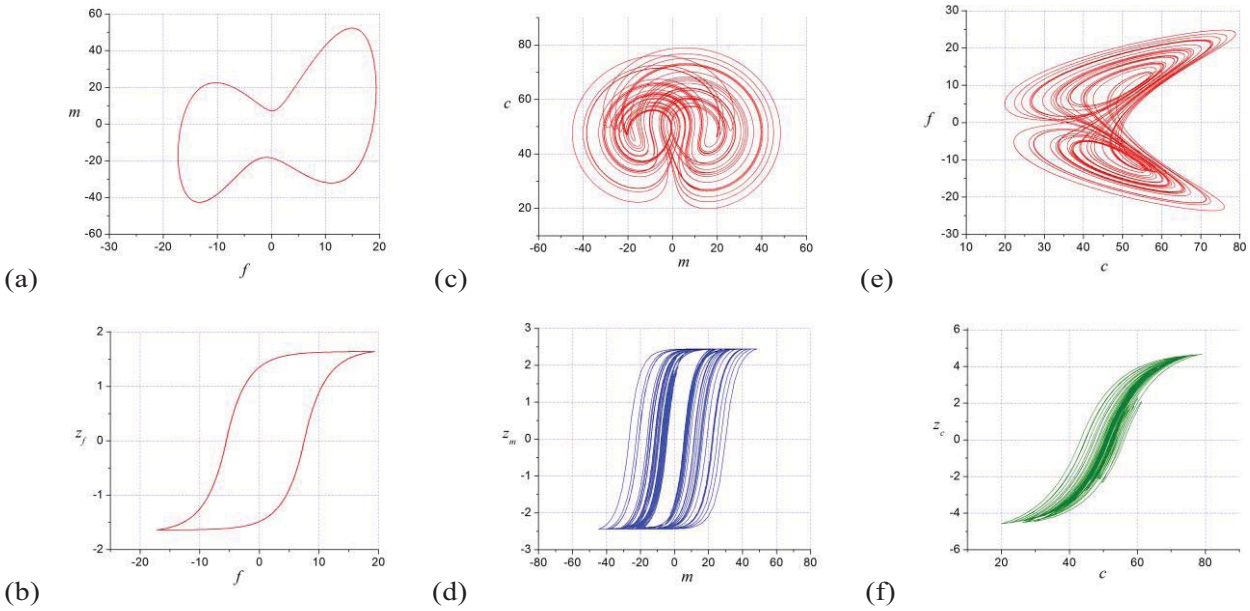

Fig. 2. Responses of the biological system with the memory of states (1)-(7) with memorization parameters h_f=0.5, h_m=0.4, h_c=0.3: (a) a chemical clock and (c),(e) chaotic attractors in MM, MDE and oxygen concentrations phase space projected to phase plane a) MDE vs MM; c) oxygen vs MDE; e) MM vs oxygen concentrations and (b),(d),(f) hysteretic loops associated with (b) MM, (d) MDE, (f) oxygen concentrations.

3 Concluding Remarks

Our numerical simulations confirmed that the suggested generalized non-linear multi-scale diffusion cancer-invasion model with additional state variables is well suited for simulations of the memory effects in the biological cancer system considered.

Analysis of the results demonstrated significant state memory influence on evolution of the conditions leading to cancer invasion in biological systems. For various memorization parameters, hysteresis loops and phase spaces projections of matrix–metalloproteinases, matrix-degradative enzymes and oxygen concentrations demonstrated a good agreement with the conditions leading to cancer invasion in biological systems. There were ascertained two effects of the memory of states: restraining and generating effects which control the conditions leading to cancer invasion in biological systems.

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