TRAVELLING WAVES AND SHAPIRO STEPS IN A TUMOR-GROWTH MODEL

Decebal VASINCU[1], Călin Gheorghe BUZEA[2], Maricel AGOP[3], Daniel TIMOFTE[4]

In a simplified approach of Ivancevic cancer growth phzsical model, we show that important features appear. A numerical analysis of this model is performed, involving travelling wave solutions for some choices of parameters. Moreover, a reduced travelling wave equations system results which exhibits an amplitude dependence on the "pseudo-period", indicating a strong nonlinearity and an characteristic increase in Shapiro steps.

Keywords: tumor evolution, traveling waves, chaotic dynamics

1. Introduction

Distinct from simple genetic diseases where an inherited mutation in a single gene is sufficient to determine the pathological phenotype, cancer, among pathogenetic diseases, has the most complex mechanism where typically numerous mutations are present. Current medical theory views the pathology of cancer as an example of a complex adaptive system whose behavior expresses the interplay between order and chaos. With some cancers, tumorigenesis is driven by chaotic behavior, while other cancers show more order in their formation. Accompanying the transformation from normal to neoplastic tissue is an overall decrease in the complexity of the cell [1-5].

Invasion methodology - tumor invasion and metastases is a complex, dynamic, multi-step process [6,7]: i) initial invasion of tumor through basement membrane; ii) movement into connective tissue surrounding tumor cells; iii) invasion of tumor cells into blood vessels; iv) circulating tumor cells are arrested

[1] Assistent Surgery Department, Biophysical Section, University of Medicine and Pharmacy "Gr. T. Popa",University str. no. 16, 700115, Iaşi, Romania

[2] Assistent Professor, National Institute of Research and Development for Technical Physics, D. Mangeron str. no. 47, Iaşi 700050, Romania

[3] Professor, Lasers, Atoms and Molecules Physics Laboratory, University of Science and Technology, Villeneuve d'Ascq, 59655, Lille, France, and Department of Physics,"Gh. Asachi" Technical University, D. Mangeron str. no. 67, Iaşi 700050, Romania,
Corresponding author email address: m.agop@yahoo.com

[4] Assistent, III Surgery Department, Hospital "Sf. Spiridon", University of Medicine and Pharmacy "Gr. T. Popa",University str. no. 16, 700115, Iaşi, Romania

in blood vessels of a distant organ or tissue; tumor cells invade organ from blood vessels; v) tumor cells then grow within tissue to form a metastatic tumor that may become clinically evident; vi) process of tumor invasion and metastases results from alterations in cell-to-cell and cell-to-matrix adhesion and increased matrix degradation. *Extracellular matrix degradation* - Several stages during the process of tumor invasion and metastases require increased degradation or breakdown of extracellular matrix or connective tissue surrounding tumor cells. The extracellular matrix is a complex mixture of proteins including different types of collagen, elastin, fibronectin, and laminin. Digestion of extracellular matrix is carried out by several groups of proteolytic enzymes [8]. *Cell adhesion* - Tumor invasion and metastasis is also characterized by alterations in both cell-to-cell and cell-to-matrix adhesion. Cellular adhesion both to adjacent cells and surrounding extracellular matrix is mediated by a variety of molecules. *Angiogenesis* - New blood vessel formation (angiogenesis) is an important factor for continued growth and development of both malignant tumors and metastases. Development of new blood vessels in tumors is stimulated by a wide variety of angiogenic factors produced by both tumor cells and stromal cells. In addition, several naturally occurring antiangiogenic factors have been identified, most notably angiostatin and endostatin. *Formation of metastases in specific tissues* - Some tissues and organs are more susceptible to the formation of metastases (e.g. liver, lung, and bone), whereas metastases are relatively uncommon in other tissues (e.g. kidney and heart). Several factors have been proposed to explain the formation of metastases in particular tissues including the expression of specific cell adhesion molecules in vascular endothelium of particular organs that are able to arrest circulating tumor cells. Another feature of metastases is the phenomenon of dormancy or latency of metastatic tumors such that many years can elapse between the diagnosis and the apparent curative treatment of the primary tumor and the clinical appearance of metastatic tumors. Dormancy appears to occur when growth of the metastatic tumor is balanced by an equivalent or even higher rate of tumor cell death by apoptosis.

The process of invasion of tissue by cancer cells is crucial for metastasis (the formation of secondary tumors) which is the main cause of mortality in patients with cancer. In the invasion process itself, adhesion, both cell-cell and cell-matrix, plays an extremely important role.

The main aims of this paper are (i) to lay the foundation for developing a new quantitative/qualitative theoretical model of tumor invasion; (ii) to mathematically investigate the importance of ECM - matrix degradative enzymes - tumor interactions in governing the migration of tumor cells [1,2]. Consequently, we propose a simplified approach of the Ivancevic cancer growth model [9]. A numerical analysis of this model is performed using computational routines for solving non-linear PDEs in Wolfram Mathematica. These results first indicate that

the model might exhibit travelling wave solutions for some choices of parameters and then it is indisputably demonstrated numerically, in a subsequent section. Finally, a reduced system of equations obtained from the above model provides some remarkable features.

2. Numerical Analysis of the Cancer Evolution Model

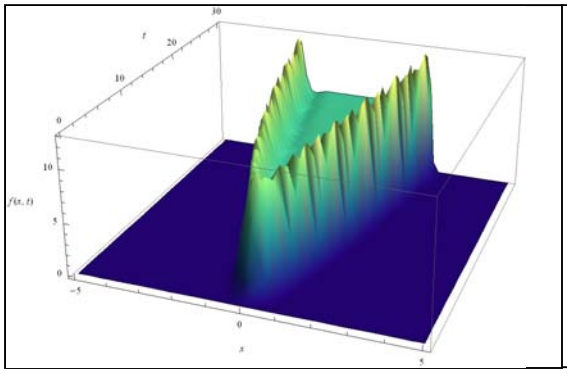
We propose the following normalized one-dimensional nonlinear system of PDEs to depict tumor progression, (Ivancevic cancer growth model [9] with constant tumor cell density):

$$\frac{\partial f}{\partial t} = k_1(m - f)\,,\ \frac{\partial m}{\partial t} = d_m \frac{\partial^2 m}{\partial x^2} + (\gamma - c) f - m\,,\ \frac{\partial c}{\partial t} = d_c \frac{\partial^2 c}{\partial x^2} + k_3 fm - k_4 c \quad \text{(1a-c)}$$

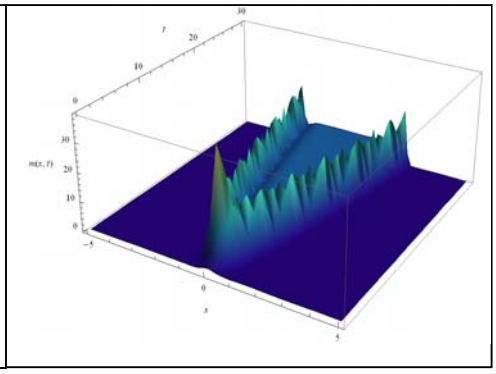
It is focused on three key variables involved in tumor cell invasion, namely MM (complex mixture of macromolecules – the extracellular material) concentration (denoted by *f*), MDE (matrix-degradative enzymes) concentration (denoted by *m*), and oxygen concentration (denoted by *c*). Each of the three variables (*f*, *m*, *c*) is a function of the spatial variable *x* and time *t*. Here $k_1 = \alpha\eta$, $k_3 = \nu$, $k_4 = \delta\phi$ where α, γ, δ, ϕ, ν, η represents tumor cell volume (proliferation/non-proliferation fraction), number of tumor cells, diffusion from the surface (saturation level), natural decay of oxygen, production of oxygen by MM, degradation of MM by MDE, respectively, d_m is the diffusion of MDE and d_c the diffusion of oxygen [9]. All these are non-dimensional parameters. Note, that even if the cell density is being modelled as a constant in Ivancevic's model, it is reintroduced into the dynamics via the cell number, γ [9]. This is a system of three diffusion equations with nonlinear source terms and is considered to hold on some spatial domain Ω (a region of tissue) with appropriate initial conditions for each variable. We assume that the oxygen and MDEs remain within the domain of tissue under consideration and therefore no-flux boundary conditions are imposed on $\partial\Omega$, the boundary of Ω.

We assume the initial MDE concentration profile is proportional to the initial tumor cell density by taking $m(x,0) = \exp(-\varepsilon x^2)$,where ε is a positive constant, the surrounding tissue was totally degraded by the tumor and the oxygen is not present ($f(x, 0) = 0$, $c(x, 0) = 0$). Also we impose periodic boundary conditions for the matrix degradative enzymes (the plasminogen activator (PA) system and the large family of matrix metalloproteinases (MMPs) that have been repeatedly implicated in all of the steps of tumor invasion and metastasis) $m(x_{\min}, t) = m(x_{\max}, t)$. The following numerical results were obtained using computational routines for solving non-linear PDEs in Wolfram Mathematica. In

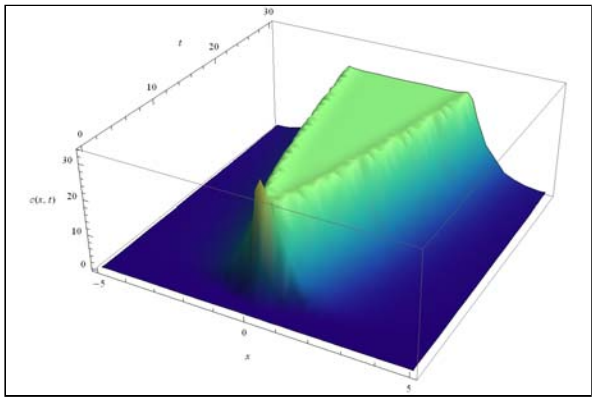
the next simulations, the parameter values used are as follows: $k_1 = 0.3$, $d_m = 0.0005$, $\gamma = 26.5$, $d_c = 0.5$, $k_3 = 0.5$, $k_4 = 1$ and $\varepsilon = 10$ (see the relationships with the constant parameters that described the system in the cancer growth model [10] and Ivancevic's model [9]. We show in Figs. 1a-c the dependence of the fields f, m and c on the space coordinate x and time coordinate t, in surface plot representations. Furthermore, Figs. 2a-c show the same above mentioned fields dependence on the coordinate x, this time for discrete values of $t = 10, 15, 20, 25, 30$.



a)

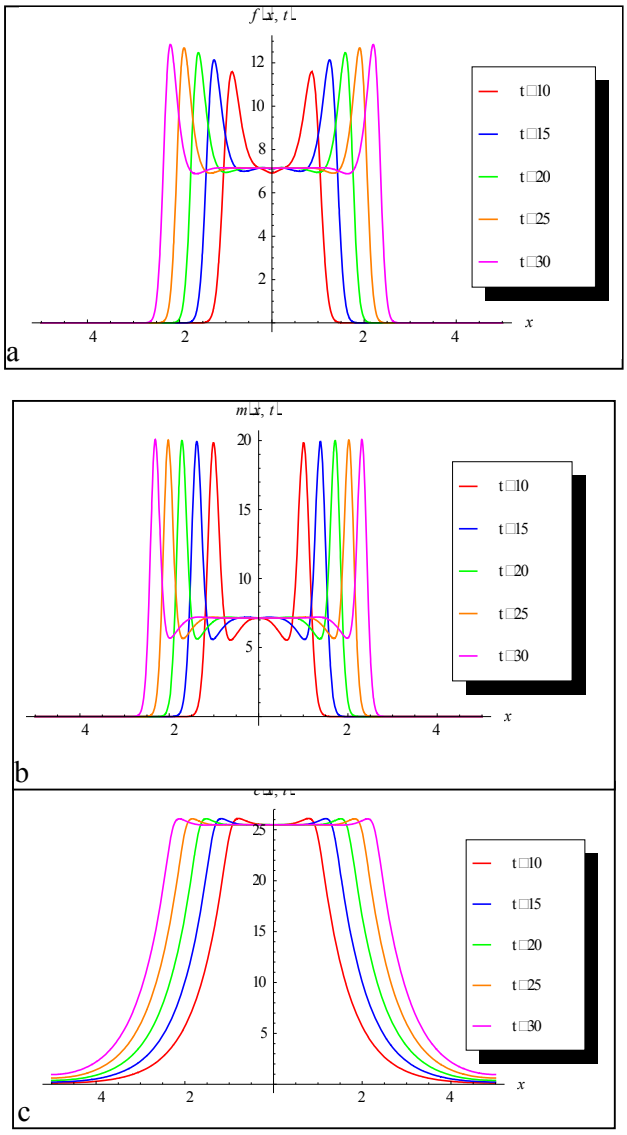


b)



c)

Figs. 1. 3D plot of the solution of (1a-c) for a) MM concentration *f(x,t)* b) MDE concentration *m(x,t)* and c) oxygen concentration *c(x,t)*.



Figs. 2. Plot of the solution of (1a-c) for a) MM concentration *f(x,t)* b) MDE concentration *m(x,t)* and c) oxygen concentration *c(x,t)* for different values of time (t = 10-30), clearly showing the presence of a traveling wave.

The followings result: i) both fields *f(x, t)* and *m(x, t)* present similar dependence on coordinates x and t – it is normal since there is a direct relationship between *f*, that represents the MM concentration and *m* , the MDE concentration – the later acts upon the former by degrading it; ii) since the fields *f(x, t)* and *m(x, t)* "bifurcate" (like in the case of Ivancevic's model [9]), it reinforces the fact that

tumors are composed of two states (i.e. proliferating (P) and quiescent (or non-proliferating) (Q) cells - tumor cells, pendulating from class P to class Q, as some parameters vary, possibly when tumor grows, or proliferation/non-proliferation fraction α (a.k.a. parameter k_1), changes); iii) exhibits travelling wave solutions, i.e. a malignant invasion of ECM by tumor released MDE occurs, for some choice of parameters.

Furthermore, if we drastically decrease the values of k_4 and k_2 (i.e. the diffusion from the surface, δ and the number of tumor cells,γ) in equation (1a, c) we can see that for a reduced k_1 (i.e. proliferation/non-proliferation factor, α) a bifurcation occurs in the *f(x, t)* field (see Fig. 3).

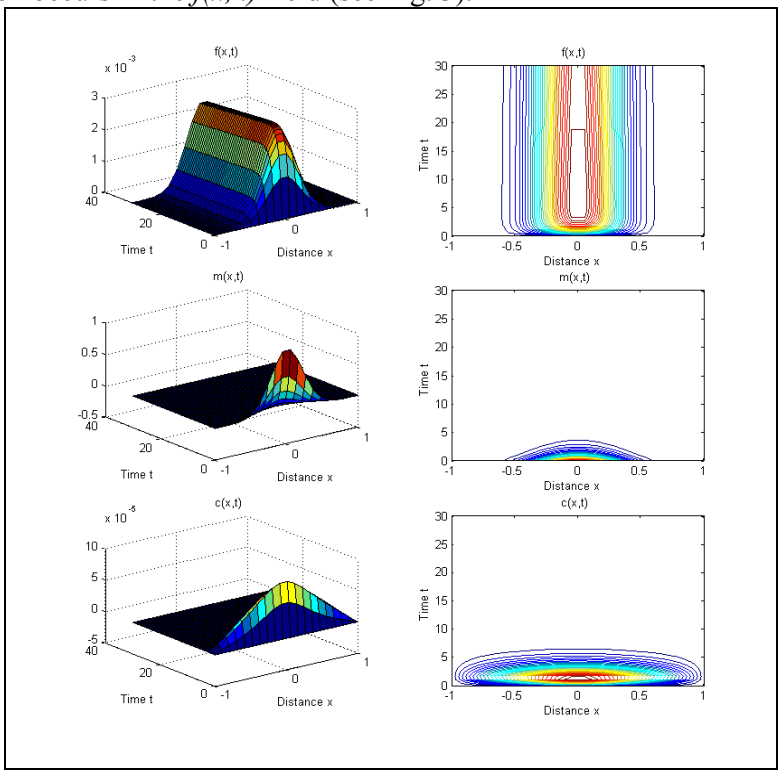


Fig. 3. Density plot of the solution of (1a-c) for a) MM concentration *f(x,t)* b) MDE concentration *m(x,t)* and c) oxygen concentration *c(x,t)* for low gamma and delta, and decreased value of k_1 (proliferating/non-proliferating factor) shows a bifurcation occurrence in the evolution of *f(x,t)*.

3. Travelling wave analysis of the cancer evolution model

The numerical simulations of the previous section indicate that the system of equations (1a-c) exhibits travelling wave solutions for some choice of parameters. Two of the main approaches for establishing travelling-wave

solutions for systems of PDEs are: (a) the geometric treatment of an appropriate phase space, where one essentially is interested in intersections between unstable and stable manifolds and (b) the Leray–Schauder (degree-theoretic) method, which employs homotopy techniques (see e.g. [11,12]). From a numerical analysis point of view, the former approach is used either in conjunction with a shooting method over a truncated domain or by trying to identify a "trivial" heteroclinic connection for some choice of parameters and then follow its deformation as the parameters are changing using numerical continuation.

In all cases the main purpose is to establish the existence of a travelling-wave solution without any available information concerning its nature. Our approach, however, is going to be "computer-assisted" in the sense that we are going to make use of the information that the numerics of the previous section can provide us.

Since we are interested in waves travelling from the left part of the domain to the right, we specify a traveling coordinate $\zeta = x - \varsigma t$, where $\varsigma > 0$ and we let: $F(\zeta) = f(x,t)$, $\mathrm{M}(\zeta) = m(x,t)$, $\mathrm{C}(\zeta) = c(x,t)$. We note that we assign the same wave velocity ς to each variable, as suggested by the numerical simulations. By substituting F, M and C into the system of equations 1a-c we get the travelling wave system of equations:

$$\varsigma \frac{dF}{d\zeta} = k_1(F - M), \quad -\varsigma \frac{dM}{d\zeta} = d_m \frac{d^2M}{d\zeta^2} + (k_2 - C)F - M,$$

$$-\varsigma \frac{dC}{d\zeta} = d_c \frac{d^2C}{d\zeta^2} + k_3 FM - k_4 C \qquad \text{(2a-c)}$$

Our intention is to profit from the phase-space methods and thus we formulate the system of equations (2a-c) as a dynamical system in $\Re^5$. In particular, by defining the new variables $M_1 = dM/d\zeta$, $C_1 = dC/d\zeta$ the system of equations (2a-c) can be formulated as:

$$\frac{d\mathbf{x}}{d\zeta} = \mathbf{f}(\mathbf{x}), \mathbf{x} = \begin{pmatrix} M_1 \\ M \\ C_1 \\ C \\ F \end{pmatrix} \in \Re^5, \mathbf{f}(\mathbf{x}) = \begin{pmatrix} -\frac{\varsigma}{d_m} M_1 - \frac{1}{d_m}(k_2 - C)F + \frac{1}{d_m} M \\ M_1 \\ -\frac{\varsigma}{d_c} C_1 - \frac{k_3}{d_c} FM + \frac{k_4}{d_c} C \\ C_1 \\ \frac{k_1}{\varsigma}(F - M) \end{pmatrix} \qquad \text{(3a-c)}$$

Since the wave velocity ς is unknown, system (3) can be regarded as a nonlinear eigenvalue problem. Several analytical methods have been developed for estimating ς in this framework [13]. However, the numerical solutions of equations (1a-c) readily yield a value of $\varsigma \approx 240$. In the analysis that follows, we therefore use this numerical estimate for ς to fix the wave speed at the constant (normalized) value of 240 and hence take ς as a fixed parameter.

The steady states of system (3) can be found by solving the (nonlinear) equation $\mathbf{f}(\mathbf{x}) = \mathbf{0}$. For the purposes of the travelling-wave analysis, the numerical simulations of the previous section indicate that we should identify a heteroclinic connection between $\mathbf{x}^{\pm 0}$ and $\mathbf{x}^1$ (the trivial solution), where (substituting the values of the constants k_1 - k_4 from the previous section):

$$\mathbf{x}^{\pm 0} = \begin{pmatrix} 0 \\ \pm\sqrt{\dfrac{k_4(k_2-1)}{k_3}} \\ 0 \\ k_2 - 1 \\ \pm\sqrt{\dfrac{k_4(k_2-1)}{k_3}} \end{pmatrix} = \begin{pmatrix} 0 \\ \pm\sqrt{51} \\ 0 \\ 25.5 \\ \pm\sqrt{51} \end{pmatrix} \qquad \mathbf{x}^1 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{4a,b}$$

We are interested in the existence of an orbit $\mathbf{x}_{con}(\zeta)$ of (3) that satisfies:

$$\lim_{\zeta \to -\infty} \mathbf{x}_{con}(\zeta) = \mathbf{x}^{\pm 0} \text{ and } \lim_{\zeta \to \infty} \mathbf{x}_{con}(\zeta) = \mathbf{x}^1 \tag{5a,b}$$

We consider the linearizations

$$\frac{d\mathbf{x}}{d\zeta} = D\mathbf{f}(\mathbf{x}^{\pm 0})\mathbf{x} \quad \text{and} \quad \frac{d\mathbf{x}}{d\zeta} = D\mathbf{f}(\mathbf{x}^1)\mathbf{x} \tag{6a,b}$$

of the vector field $\boldsymbol{f}$ at equilibria $\boldsymbol{x}^{\pm 0}$ and $\boldsymbol{x}^1$, respectively. It is a straightforward task to determine the spectrum of the Jacobian matrices $D\boldsymbol{f}(\boldsymbol{x}^{\pm 0})$ and $D\boldsymbol{f}(\boldsymbol{x}^1)$. Indeed, there are three real and two complex conjugate eigenvalues of $D\boldsymbol{f}(\boldsymbol{x}^0)$ (we kept only the positive of the two $\boldsymbol{x}^{\pm 0}$ steady states, since we got the same eigenvalues for both $D\boldsymbol{f}(\boldsymbol{x}^{\pm 0})$), among the real ones, one is positive and two negative, with the positive eigenvalue implying the existence of a three-dimensional *unstable* manifold $W^u(\boldsymbol{x}^0)$. Furthermore, there are five real eigenvalues of $D\boldsymbol{f}(\boldsymbol{x}^1)$, two positive and three negative, with the negative ones implying the existence of a three-dimensional *stable* manifold $W^s(\boldsymbol{x}^1)$. We note that

$$\dim\left(W^u\left(\mathbf{x}^0\right)\right) + \dim\left(W^s\left(\mathbf{x}^1\right)\right) = \dim \Re^5 + 1 \tag{7}$$

Equation (7) suggests that $W^u(\mathbf{x}^0)$ and $W^s(\mathbf{x}^1)$ probably intersect transversally along a one-dimensional curve in the five-dimensional phase-space [14,15]. If this is the case then this curve would define a (generic) heteroclinic connection.

Now, if from (2a) we separate M to get

$$M = F - \frac{\varsigma}{k_1}\frac{dF}{d\zeta} \tag{8}$$

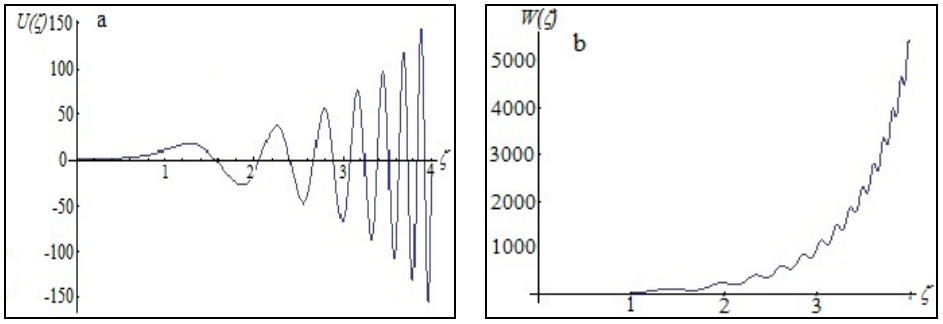
we reduce the system of equations (2a-c) to

$$\begin{aligned} &-\frac{\varsigma d_m}{k_1}\frac{d^3F}{d\zeta^3} + \left(d_m - \frac{\varsigma^2}{k_1}\right)\frac{d^2F}{d\zeta^2} + \varsigma\left(1+\frac{1}{k_1}\right)\frac{dF}{d\zeta} + (k_2-1)F - FC = 0 \\ &d_c\frac{d^2C}{d\zeta^2} + \varsigma\frac{dC}{d\zeta} - k_4C + k_3F^2 - \frac{k_3\varsigma}{k_1}F\frac{dF}{d\zeta} = 0 \end{aligned} \tag{9a,b}$$

The numerical results were obtained using computational routines for solving non-linear PDEs in Wolfram Mathematica.

Fig. 4a shows the dependence of the field F (the MM concentration) on the travelling coordinate ζ. It can be seen an overall increase of F with the increase of ζ and moreover, an increase of the amplitude of F with the decrease of the "pseudo-period" of ζ. The amplitude dependence of the "pseudo-period" indicates that we deal with a strongly nonlinear system, characteized by by multiple stable and/or unstable states, similar with [16].

In Fig. 4b we show the dependence of the field C (oxygen concentration) on the coordinate ζ. It results an increase of C with the increase of ζ and moreover, an interesting increase in Shapiro steps can be detected in the dynamics of this field.



Figs. 4. Plot of the solution (9a,b) for a) MM concentration $F(\zeta)$ and b) oxygen concentration $C(\zeta)$. Note the Shapiro steps occurring in the oxygen concentration dependence on the travelling coordinate ζ.

The dependences illustrated in Figs.4 are useful in practical applications because they offer important information in controlling the tumor grows dynamics or in chaos inhibition [17]. Moreover, the identification of the critical parameter for a specific dynamics is an important step in the construction of the characteristic time-series for further proccesing and data analysis using new methods of investigation, as those in [18,19].

4. Conclusions

We introduce a simplified approach of Ivancevic cancer growth model with constant tumor cell density which includes some interesting features.

From the numerical analysis performed on the newly introduced model the followings results can be detailed. First, both fields *f(x, t)* and *m(x, t)* present similar dependence on coordinates *x* and *t.* Second, since the fields *f(x, t)* and *m(x, t)* "bifurcate", it may be reinforced the fact that tumors are composed of a proliferating (*P*) and a quiescent (or non-proliferating) (*Q*) state, pendulating from class *P* to class *Q*, as some parameters vary. Third, the solutions exhibit travelling wave behaviors, for some choice of parameters. Moreover, if we drastically decrease the values of k_4 and k_2 (i.e. the diffusion from the surface, δ and the number of tumor cells, γ) in equation (1a,c) we can see that for a reduced k_1 (i.e. proliferation/non-proliferation factor, α) a bifurcation occurs in the *f(x, t)* field (Fig. 3). A travelling wave analysis of the new cancer growth model established the existence of a travelling-wave solution without any available information concerning its nature.

Furthermore, after working out a reduced travelling wave equations system (9a,b), from (2a-c), an amplitude dependence of the "pseudo-period" indicating a strongly nonlinear system and an interesting increase in Shapiro steps (appearing in voltage-current characteristics ac-driven Josephson junctions, superconducting nanowires etc.) can be detected in the dynamics.

In order to develop theoretical models we must admit that the biological system that displays chaotic behaviour are recognized to acquire self-similarity (space-time structures seem to appear) in association with strong fluctuations at all possible space-time scales. Then, for temporal scales that are large with respect to the inverse of the highest Lyapunov exponent, the deterministic trajectories are replaced by a collection of potential trajectories and the concept of definite positions by that of probability density. Therefore a complete analysis could implies the non-differentiable formalism of the scale relativity theory [20,21] as in [22].

REFERENCES

[1] *J.O.'.D. McGee, P.G. Isaacson, N.A. Wright* (Eds.), Oxford Textbook of Pathology. Oxford University Press, Oxford, 1992

[2] *V. Kumar, A.K. Abbas, N. Fausto, Robbins and Cotran*, Pathologic Basis of Disease, fourth ed., W.B. Saunders Co., 2004

[3] *M.A.J. Chaplain, B.D. Sleeman*, A mathematical model for the production and secretion of tumour angiogenesis factor in tumours, IMA J. Math. Appl. Med. Biol. **7**, pp. 93-108, 1990

[4] *M.A.J. Chaplain, A.M. Stuart*, A mathematical model for the diffusion of tumour angiogenesis factor into the surrounding host tissue, IMA J. Math. Appl. Med. Biol. 8, pp. 191-220, 1991

[5] *M.A.J. Chaplain, B.D. Sleeman*, Modelling the growth of solid tumours and incorporating a method for their classification using nonlinear elasticity theory, J. Math. Biol. 31, pp. 431-479, 1993

[6] *D. Trucu, P. Lin, M.A.J. Chaplain, Y. Wang*, A multiscale moving boundary model arising in cancer invasion, Multiscale Model. Simul. 11, pp. 309-335, 2013

[7] *N.E. Deakin, M.A.J. Chaplain*, Mathematical modeling of cancer invasion: the role of membrane-bound matrix metalloproteinases, Front. Oncol. 3, 70, 2013

[8] *D.K. Schlueter, I. Ramis-Conde, M.A.J. Chaplain*, Computational modeling of single-cell migration: The leading role of extracellular matrix fibers, Biophys. J. 103, pp. 1141-1151, 2012

[9] *T.T. Ivancevic, M. J. Bottema, and L. C. Jain*, A Theoretical Model of Chaotic Attractor in Tumor Growth and Metastasis, arXiv: 0807.4272 in Cornell University Library's arXiv.org, 2008

[10] *A.R.A., Anderson*, A hybrid mathematical model of solid tumour invasion: the importance of cell adhesion., Math. Med. Biol. 22, pp. 163–186, 2005

[11] *H. Berestycki, B. Larrouturou, P.L. Lions*, Multi-dimensional travelling wave solutions of a flame propagation model, Arch. Rational Mech. Anal. 111, pp. 33–49, 1990

[12] *A.I. Volpert, V.A. Volpert, V.A. Volpert*, Traveling Wave Solutions of Parabolic Systems, Translations of Mathematical Monographs, **vol. 140**, American Mathematical Society, 2000

[13] *V. Volpert, S. Petrovskii*, Reaction–diffusion waves in biology, Physics of Life Reviews 6, pp. 267–310, 2009.

[14] *P.B. Ashwin, M.V. Bartuccelli, T.J. Bridges, S.A. Gourley*, Travelling fronts for the KPP equation with spatio-temporal delay, Z. Angew. Math. Phys. 53, pp. 103–122, 2002

[15] *J. Guckenheimer, P. Holmes*, Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields, Applied Mathematical Sciences, **vol. 42**, Springer, 1983, corrected seventh printing, 2002

[16] *C. Stan***,** Qualitative approach on the multiple states in the electrical discharge plasma*,* , Buletinul Institutului Politehnic Din Iasi, Sectia Matematica, Mecanica Teoretica, Fizica Tom Xlvix(Liii), Fasc. 1-2, 17-25, 2003.

[17] *C. Stan, C.P. Cristescu, M. Agop*, Golden mean relevance for chaos inhibition in a system of two coupled modified van der Pol oscillators, Chaos, Solitons and Fractals **31**, pp. 1035-1040, 2007.

[18] *C. Stan, C.P.Cristescu, D.G. Dimitriu*, Analysis of the intermittent behavior in a low-temperature discharge plasma by recurrence plot quantification, Physics of Plasmas **17**, art. no.042115, 2010.

[19] *C. Stan, C.P. Cristescu, D.A. Neacşu*, Using chaos game representation for similarity studies on albumin amino acids sequences, Revue Roumaine de Chimie **57**, pp. 45-48, 2012.

[20] *Gottlieb, M. Agop, G. Ciobanu*, El Naschie'sepsilon ((infinity)) space-time and new results in scale relativity theories, Chaos Solitons & Fractals, **vol. 9**, Issue 2, pp. 380-398, DOI: 10.1016/j.chaos.2005.11.018, oct. 2006

[21] *M. Agop, O. Niculescu, A. Timofte, L Bibire, A.S. Ghenadi, A. Nicuta, C. Nejneru, G.V. Munceleanu*, Non-Differentiable Mechanical Model and Its Implications, International Journal of Theoretical Physics 7, **vol. 49**, pp. 1489-1506, 2010

[22] *C.Gh. Buzea, M. Agop, E. Moraru, B.A. Stana, M. Gîrțu, D. Iancu*, Some implications of Scale Relativity theory in avascular stages of growth of solid tumors in the presence of an immune system response, Journal of Theoretical Biology 282, pp. 52-64, 2011