BULETINUL INSTITUTULUI POLITEHNIC DIN IAŞI
Publicat de
Universitatea Tehnică „Gheorghe Asachi” din Iaşi
Volumul 67 (71), Numărul 3, 2021
Secţia
MATEMATICĂ. MECANICĂ TEORETICĂ. FIZICĂ

A TUMOR GROWTH MODEL WITH A „BUTTERFLY” – TYPE CHAOTIC TIME ATTRACTOR. CANCER EVOLUTION THROUGH A TRAVELING WAVES-TYPE MECHANISM

BY

IRINA BUTUC[1], VLAD GHIZDOVĂŢ[2,*], CRISTINA-MARCELA RUSU[3] and CĂLIN GHEORGHE BUZEA[4]

[1]“Alexandru Ioan Cuza” University of Iaşi,
Faculty of Physics, Iaşi, Romania
[2]“Grigore T. Popa” University of Medicine and Pharmacy,
Faculty of Medicine, Biophysics and Medical Physics Department, Iaşi, Romania
[3]“Gheorghe Asachi” Technical University of Iaşi,
Department of Physics, Iaşi, Romania
[4]National Institute of Research and Development for Technical Physics, Iaşi, Romania

Received: August 3, 2021
Accepted for publication: September 7, 2021

Abstract. In this paper we propose a new tumor growth model, based on the original model developed by Anderson-Chaplain to which we attached Ivancevic’s “butterfly” time attractor. The chaotic behavior provides a more realistic perspective on tumor growth, with uncertainties and uncontrollable long term stochastic effects.

Keywords: tumor growth; cancer evolution; traveling waves.

1. Introduction

Researchers are more and more expressing the idea that cancer is a genetic disease. The main cause of this diseases is an abnormal gene expression. The usual genetic diseases are caused by a single-gene mutation, whilst cancer

*Corresponding author; *e-mail*: vlad.ghizdovat@umfiasi.ro

is the result of a multitude of such mutations. Consequently, it can be regarded as a group of diseases with identical biological features. Moreover, cancer acts as a particular structure, oscillating between order and chaos. Therefore, some types of cancer can show a regular behavior, while other types display chaotic biological evolutions.

A series of resolution scales can be observed in cancer evolution, as follows (Kozusko and Bourdeau, 2007):

i) Invasion. Tumoral invasion and metastasis are complex, dynamic, and multistage processes. According to literature, any type of tumor can invade surrounding tissues through complex dynamic processes. The first step consists in tumoral invasion through the basal cell membrane, followed by diffusion in the adjacent tissue. The second step is the aggression of tumor cells on blood vessels, followed by malign pathology. This is the earliest stage that can be clinically detected. Afterwards, the tumor evolves in the tissue and generates metastasis, more specifically destabilizing cell – cell and cell – matrix connections, as well as the obvious destruction of the matrix.

ii) Extracellular matrix degeneration. The extracellular matrix (ECM) is composed of proteins such as collagen, elastin, laminin and fibronectin. The proteolytic enzymes are the ones responsible for extracellular matrix digestion. When the tumor invades, leading to metastasis, the ECM and connecting tissues are severely damaged.

iii) Cell adhesion. In the case of tumor invasion, cell – cell and cell – matrix adhesions are affected. Cellular adhesion depends on the surrounding ECM through different types of molecules.

iv) Angiogenesis. The constant growth of malign tumors, as well as metastasis evolution are the result of new blood vessels (angiogenesis). This process can be amplified by driving factors, in the case of tumor cells as well as in the case of stromal, angiostatin and endostatin cells.

v) Metastasis formation in different tissues. Several organs and tissues, such as the liver, lungs or bones, are more susceptive to metastasis formation, while other show a higher degree of resistance (the kidneys, the heart). A series of factors are responsible for this phenomenon. These are mostly represented by manifestations of several characteristic molecules, responsible for cell adhesion in the vascular endothelium of organs that fixate moving tumor cells. In some cases, metastasis do not manifest for several years, and correspondingly patients do not show symptoms for a longer period. This is the case for metastasis influenced by a cell death coefficient equal or higher than the division coefficient, through apoptosis. Tumoral invasion of different tissues is the main cause of death for cancer patients. Both types of adhesion (cell – cell and cell – matrix) are very important for the invasion process.

In this paper we propose a new tumor growth model, based on the original model developed by Anderson-Chaplain (the AC model) (Anderson *et al*., 2000) to which we attached Ivancevic's "butterfly" time attractor (Ivancevic

et al., 2008). In this way, we believe that the chaotic behavior can provide a more realistic perspective on tumor growth, with uncertainties and uncontrollable long term stochastic effects. At the same time, a tumor can grow according to its initial conditions.

2. Mathematical Model

Dedicated studies have shown that cancer cells are capable to adapt and, consequently, survive. Cancer cells can change their metabolism, from an aerobic metabolism to an anaerobic one (Liu *et al*., 2007; Brahimi-Horn and Pouyssegur, 2007), therefore being able to survive in hypoxic media. Research has shown that the tissue encompassing a tumor is oxygen, nutrient and glucose deficient, and is generally characterized by a low pH (Witz and Levy-Nissenbaum, 2006; Cuvier *et al*., 1997).

Taking the above into consideration, we propose a one-dimensional partial differential equations nonlinear system with the purpose of illustrating tumor growth.

$$\begin{aligned} \frac{\partial f}{\partial t} &= k_1(m - f) \\ \frac{\partial m}{\partial t} &= d_m \frac{\partial^2 m}{\partial x^2} + (k_2 - c) f - m \\ \frac{\partial c}{\partial t} &= d_c \frac{\partial^2 c}{\partial x^2} + k_3 fm - k_4 c \end{aligned} \tag{1}$$

Such a system includes three diffusion equations with nonlinear terms. They are likely to sustain a space domain Q (tissue area) with favorable primary conditions for each variable. The oxygen and matrix degrading enzymes (MDEs) do not change in the tissue. Consequently, no-flux boundary conditions will be considered on $\partial\Omega$, the boundary of Ω. The scale domain is the unit interval [0, 1] in one space dimension. According to our opinion, a cluster of cells initially occurs the moment the tumor gathers around $x = 0$.

$$m(x, 0) = \exp(-\varepsilon x^2) \tag{2}$$

At the same time, the primary MDE concentration profile is proportional to the initial tumor cell density, according to $m(x,0) = \exp(-\varepsilon x^2)$ where ε is a positive constant. The surrounding tissue is entirely altered by the tumor itself, in the absence of oxygen ($f(x, 0) = 0$, $c(x, 0) = 0$).

$$m(x_{\min}, t) = m(x_{\max}, t) \tag{3}$$

The periodic boundary conditions for the matrix degradative enzymes in all tumor invasion stages as well as in metastasis) should be considered periodically.

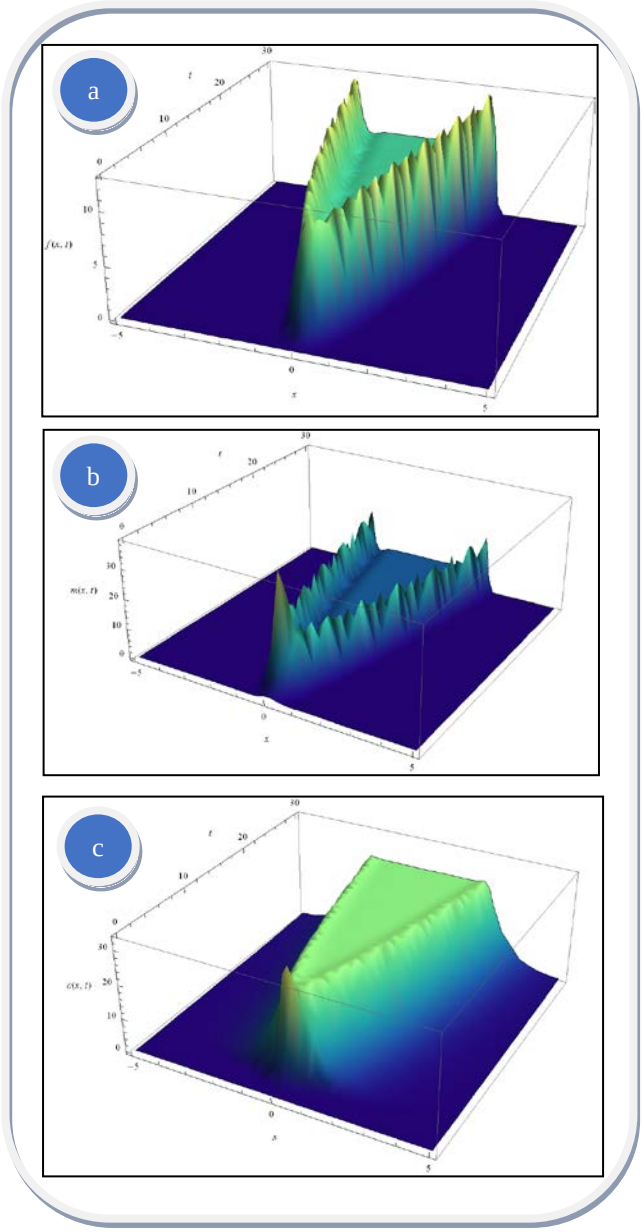


Fig. 1 – Density and 3D plot of the solution of Eq. (1) for (a) macromolecules and non-cellular material complex mix (MM) concentration $f(x, t)$; (b) MDE concentration $m(x, t)$; (c) oxygen concentration $c(x, t)$.

Our tests have shown the following results via PC routines for non-linear PDEs in Wolfram Mathematica. Parameter values: $k_1 = 0.3$, $d_m = 0.0005$, $k_2 = 26.5$, $d_c = 0.5$, $k_3 = 0.5$, $k_4 = 1$ and $\varepsilon = 10$ (see the relationship with constant parameters of the system in the previous section). Figs. 1a-c exhibit the way in which fields *f*, m and c depend on space coordinate *x* as well as on time coordinate t, according to parametric and surface image.

Consequently, we have obtained: i) fields $f(x, t)$ and $m(x, t)$ are similarly dependent on coordinates *x* and *t*, as a result of the direct relationship between *f* (MM concentration) and *m* (MDE concentration). MM concentration alters the MDE one; ii) tumors are made up of two states, the proliferating state, (P) and the quiescent, or non-proliferating one, (Q). This is a consequence of split fields $f(x, t)$ and $m(x, t)$. Tumor cells migrate between classes P and Q.

We have used the space-time system of PDE rate, to which Ivancevic's et al. simplified normalized time dependent derivative model was attached. Our model resembles the original AC pattern.

Our research reveals that fields $f(x, t)$ and $m(x, t)$ are both dependent on coordinates *x* and *t*. The two splitting fields certify that any tumor has two states: the proliferating (P) state and the quiescent (or non-proliferating) (Q) one. As long as there is a parameter variation, tumors can migrate from one state to another.

In Figs. 2a-c we can observe a travelling wave mechanism for tumor growth (Perumpanani *et al*., 1999; Marchant *et al*., 2001).

Now, if we significantly 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 Eq. (1) we can observe a bifurcation in the $f(x, t)$ field, for a reduced k_1 (*i.e*., proliferation/non-proliferation factor, α) (see Figs. 3a-c). The presence of both states (P and Q) implies the fact that the "medium" behaves like a bi-steady system (see the active media of lasers).

Because we are interested in waves travelling from the left of the domain to its right, we can define a traveling coordinate $\zeta = x - \varsigma t$, where $\varsigma > 0$ and we will get:

$$F(\zeta) = f(x,t),\ M(\zeta) = m(x,t),\ C(\zeta) = c(x,t) \tag{4}$$

Let us note that we have assigned the same wave velocity ς to each variable, according to numerical simulations. By substituting *F*, *M* and *C* into the system of Eqs. (1) we can obtain the travelling wave system of equations:

$$\begin{aligned} &\varsigma \frac{dF}{\zeta} = k_1(F - M),\ -\varsigma \frac{dM}{d\zeta} = d_m \frac{d^2M}{d\zeta^2} + (k_2 - C)F - M, \\ &-\varsigma \frac{dC}{d\zeta} = d_c \frac{d^2C}{d\zeta^2} + k_3 FM - k_4 C \end{aligned} \tag{5}$$

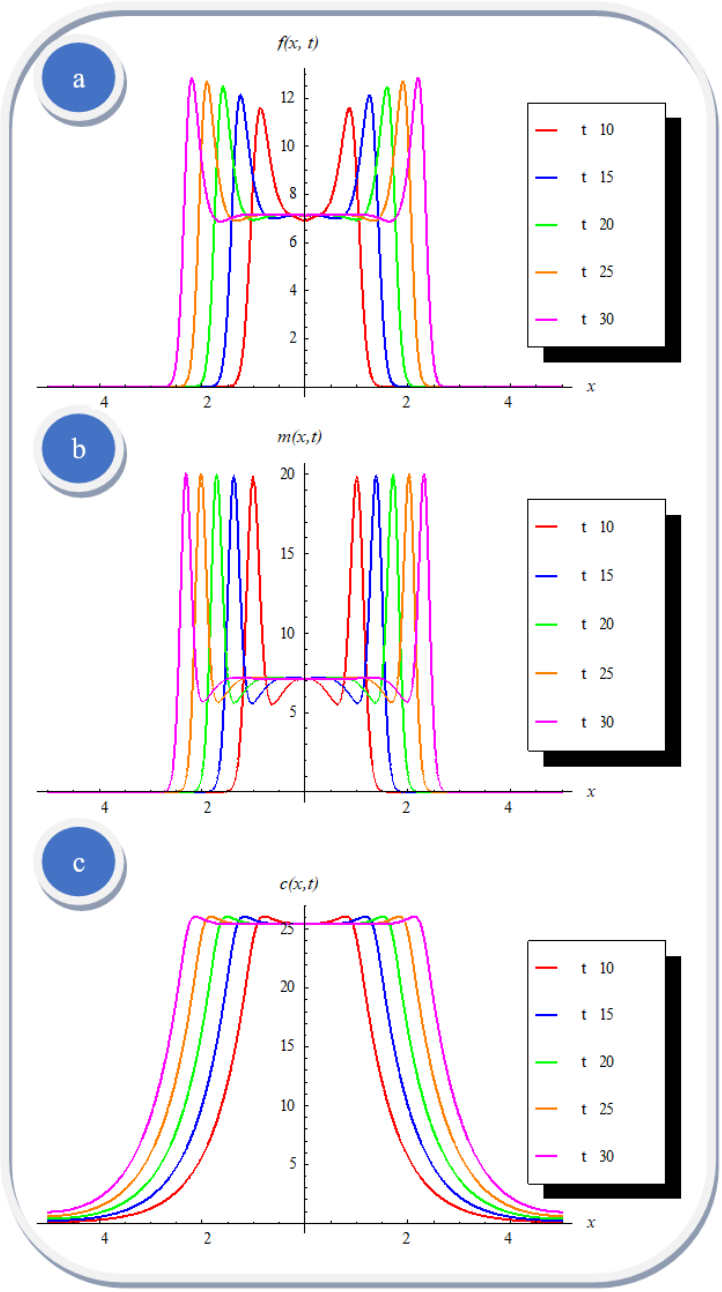


Fig. 2 – Plot of the solution of Eq. (1) for (a) MM concentration *f(x,t)*; (b) MDE concentration *m(x,t)*; (c) oxygen concentration *c(x,t)* for different time values (t = 10-30). We can highlight here the presence of a travelling wave.

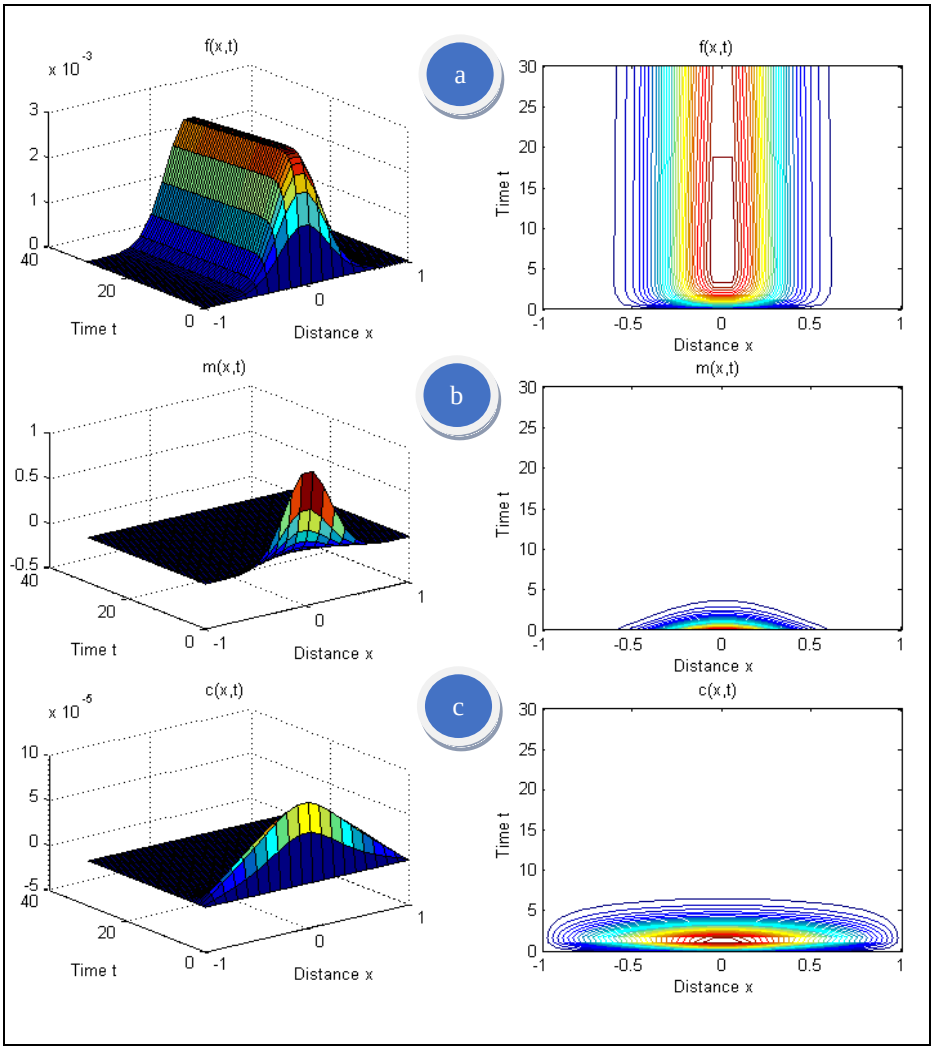


Fig. 3 – Density plot of the solution of Eq. (1) for (a) MM concentration $f(x,t)$; (b) MDE concentration $m(x,t)$; (c) oxygen concentration $c(x,t)$ for low gamma and delta, and decreased value of k_1 (proliferating/non-proliferating factor) shows a bifurcation occurrence in the evolution of $f(x,t)$.

We want to employ the phase-space methods and therefore we will formulate the system of Eqs. (5) as a dynamical system in $\mathcal{R}^5$. In particular, by defining some new variables $M_1 = dM / d\zeta$, $C_1 = dC / d\zeta$ the system of Eqs. (5) can be formulated as:

$$\frac{d\mathbf{x}}{d\zeta}=\mathbf{f}(\mathbf{x}),\mathbf{x}=\begin{pmatrix}M_1\\M\\C_1\\C\\F\end{pmatrix}\in\Re^5,\mathbf{f}(\mathbf{x})=\begin{pmatrix}-\frac{\varsigma}{d_m}M_1-\frac{1}{d_m}(k_2-C)F+\frac{1}{d_m}M\\M_1\\-\frac{\varsigma}{d_c}C_1-\frac{k_3}{d_c}FM+\frac{k_4}{d_c}C\\C_1\\\frac{k_1}{\varsigma}(F-M)\end{pmatrix} \tag{6}$$

Because the wave velocity ς is unknown, system (6) can be approached as a nonlinear eigenvalue problem. Some analytical methods can be found for estimating ς in this context. However, the numerical solutions of Eqs. (6) easily yield a value of $\varsigma \approx 240$. We will therefore use this numerical estimate for ς to fix the wave velocity at the constant (normalized) value of 240 and thus take ς as a fixed parameter.

We can find the steady states of system (6) by solving equation $\mathbf{f}(\mathbf{x})= \mathbf{0}$. Taking into account the scope of a travelling-wave analysis, the previous numerical simulations indicate that a heteroclinic connection between $\mathbf{x}^{\pm 0}$ and $\mathbf{x}^1$ (the trivial solution) should be identified, where (substituting the values of the constants k_1- k_4 from the previous section):

$$\mathbf{x}^{\pm 0}=\begin{pmatrix}0\\\pm\sqrt{\frac{k_4(k_2-1)}{k_3}}\\0\\k_2-1\\\pm\sqrt{\frac{k_4(k_2-1)}{k_3}}\end{pmatrix}=\begin{pmatrix}0\\\pm\sqrt{51}\\0\\25.5\\\pm\sqrt{51}\end{pmatrix}\quad \mathbf{x}^1=\begin{pmatrix}0\\0\\0\\0\\0\end{pmatrix} \tag{7}$$

We are now seeking an orbit $\mathbf{x}_{con}(\zeta)$ of (6) that satisfies:

$$\lim_{\zeta\to-\infty}\mathbf{x}_{con}(\zeta)=\mathbf{x}^{\pm 0} \text{ and } \lim_{\zeta\to\infty}\mathbf{x}_{con}(\zeta)=\mathbf{x}^1 \tag{8}$$

We consider the linearization

$$\frac{d\mathbf{x}}{d\zeta}=D\mathbf{f}(\mathbf{x}^{\pm 0})\mathbf{x} \quad \text{and} \quad \frac{d\mathbf{x}}{d\zeta}=D\mathbf{f}(\mathbf{x}^1)\mathbf{x} \tag{9}$$

of the vector field $\boldsymbol{f}$ at equilibria $\boldsymbol{x}^{\pm 0}$ and $\boldsymbol{x}^1$. We are now aiming to determine the spectrum of the Jacobian matrices $D\boldsymbol{f}(\boldsymbol{x}^{\pm 0})$ and $D\boldsymbol{f}(\boldsymbol{x}^1)$. 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 are negative, with the positive

eigenvalue leading to a three-dimensional *unstable* manifold $W^u(\boldsymbol{x}^0)$. There are five real eigenvalues of $D\boldsymbol{f}(\boldsymbol{x}^1)$, two positive and three negative, with the negative ones leading to a three-dimensional *stable* manifold $W^s(\boldsymbol{x}^1)$. Let us note that

$$\dim\left(W^u\left(\mathbf{x}^0\right)\right)+\dim\left(W^s\left(\mathbf{x}^1\right)\right)=\dim\Re^5+1 \tag{10}$$

Eq. (10) shows that $W^u(\boldsymbol{x}^0)$ and $W^s(\boldsymbol{x}^1)$ probably intersect transversally along a one-dimensional curve in the five-dimensional phase-space. In this case the curve would define a heteroclinic connection.

If from the first Eq. (5) we separate M to obtain

$$M = F - \frac{\varsigma}{k_1}\frac{dF}{d\zeta} \tag{11}$$

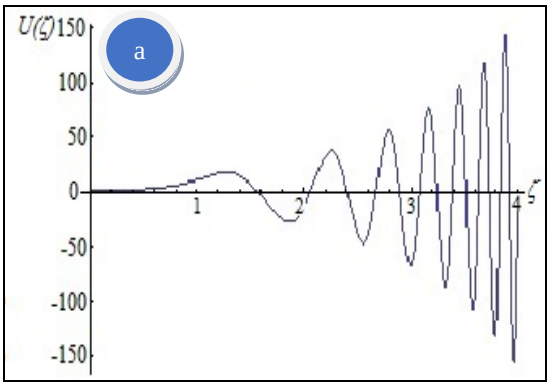
the system of Eqs. (5) can be reduced to

$$\begin{aligned} &-\frac{\varsigma d_m}{k_1}\frac{d^3F}{d\zeta^3}+\left(d_m-\frac{\varsigma^2}{k_1}\right)\frac{d^2F}{d\zeta^2}+\varsigma\left(1+\frac{1}{k_1}\right)\frac{dF}{d\zeta}+(k_2-1)F-FC=0 \\ &d_c\frac{d^2C}{d\zeta^2}+\varsigma\frac{dC}{d\zeta}-k_4C+k_3F^2-\frac{k_3\varsigma}{k_1}F\frac{dF}{d\zeta}=0. \end{aligned} \tag{12}$$

3. Results

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

Fig. 4a shows the dependence of the field F (the MM concentration) on the travelling coordinate ζ. We want to highlight here 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" shows us that we are dealing with a strongly nonlinear system, characterized by multiple stable and/or unstable states.



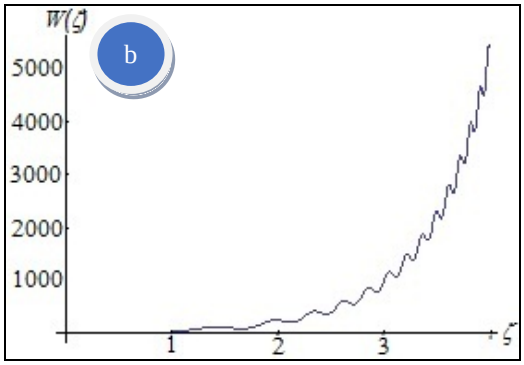


Fig. 4 – Plot of the solution (12) for (a) MM concentration $F(\zeta)$ and (b) oxygen concentration $C(\zeta)$. We can see Shapiro steps occurring in the oxygen concentration dependence on the travelling coordinate ζ.

4. Conclusions

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

These dependences are useful in practical applications because they offer important information in controlling and limiting the tumor growth dynamics.

The behaviors presented above (especially the presence of Shapiro steps) specifies the fact that the "media" signals the presence of coherence (it can be considered as an active media like lasers)

REFERENCES

Anderson A.R.A., Chaplain M.A.J., Newman E.L., Steele R.J.C., Thompson A.M., *Mathematical Modelling of Tumour Invasion and Metastasis*, Computational and Mathematical Methods in Medicine **2**, 129-154 (2000).

Brahimi-Horn M.C., Pouyssegur J., *Oxygen, a Source of Life and Stress*, FEBS Letters **581**, *19*, 3582-3591 (2007).

Cuvier C., Jang A, Hill R.P., *Exposure to Hypoxia, Glucose Starvation and Acidosis: Effect on Invasive Capacity of Murine Tumor Cells and Correlation with Cathepsin (L + B) Secretion*, Clinical & Experimental Metastasis **15**, *1*, 19-25 (1997).

Ivancevic T.T., Bottema M.J., Jain L.C., *A Theoretical Model of Chaotic Attractor in Tumor Growth and Metastasis*, arXiv:0810.4580v1 (2008).

Kozusko F., Bourdeau M., *A Unified Model of Sigmoid Tumour Growth Based on Cell Proliferation and Quiescence*, Cell Proliferation **40**, *6*, 824-834 (2007).
Liu C., Gao S., Zhang L., *Tumor Microenvironment: Hypoxia and Buffer Capacity for Immunotherapy*, Medical Hypotheses **69**, *3*, 590-595 (2007).
Marchant B.P., Norbury J., Sherratt J.A., *Travelling Wave Solutions to a Haptotaxis-Dominated Model of Malignant Invasion*, Nonlinearity **14**, 1653-1671 (2001).
Perumpanani A.J., Norbury J., Sherratt J.A., Byrne H.M., *Traveling Shock Waves Arising in a Model of Malignant Invasion*, Physica D **126**, 145-159 (1999).
Witz I.P., Levy-Nissenbaum O., *The Tumor Microenvironment in the Post-PAGET Era*, Cancer Letters **242**, *1*, 1-10 (2006).

PROCEDURI OPERAȚIONALE ÎN DINAMICILE SISTEMELOR COMPLEXE

(Rezumat)

În prezenta lucrare se propune un nou model de creștere tumorală, bazat pe cel original Anderson-Chaplain, la care s-a atașat atractorul de timp tip „fluture” al lui Ivancevic. Astfel, comportamentul haotic oferă o perspectivă mai realistă asupra creșterii tumorale, cu incertitudini și efecte stocastice pe termen lung.