A Mathematical Model of Chaotic Attractor in Tumor Growth and Decay

Tijana T. Ivancevic, Murk J. Bottema and Lakhmi C. Jain

Abstract—We propose a strange-attractor model of tumor growth and metastasis. It is a 4-dimensional spatio-temporal cancer model with strong nonlinear couplings. Even the same type of tumor is different in every patient both in size and appearance, as well as in temporal behavior. This is clearly a characteristic of dynamical systems sensitive to initial conditions. The new chaotic model of tumor growth and decay is biologically motivated. It has been developed as a live Mathematica demonstration, see Wolfram Demonstrator site:

http://demonstrations.wolfram.com/ChaoticAttractorInTumorGrowth/

Index Terms—Reaction-diffusion tumor growth model, chaotic attractor, sensitive dependence on initial tumor characteristics

I. INTRODUCTION

Cancer is one of the main causes of morbidity and mortality in the world. There are several different stages in the growth of a tumor before it becomes so large that it causes the patient to die or reduces permanently their quality of life. Developed countries are investing large sums of money into cancer research in order to find cures and improve existing treatments. In comparison to molecular biology, cell biology, and drug delivery research, mathematics has so far contributed relatively little to the area [1]. A number of mathematical models of avascular (solid) tumor growth were reviewed in [2]. These were generally divided into continuum cell population models described by diffusion partial differential equations (PDEs) of continuum mechanics [3], [4] combined with chemical kinetics, and discrete cell population models described by ordinary differential equations (ODEs).

On the other hand, in many biological systems it is possible to empirically demonstrate the presence of attractors that operate starting from different initial conditions [5]. Some of these attractors are points, some are closed curves, while the others have non-integer, fractal dimension and are termed "strange attractors" [6]. It has been proposed that a prerequisite for proper simulating tumor growth by computer is to establish whether typical tumor growth patterns are fractal. The fractal dimension of tumor outlines was empirically determined using the box-counting method [7]. In particular, fractal analysis of a breast carcinoma was performed using a morphometric method, which is the box-counting method applied to the mammogram as well as to the histologic section of a breast carcinoma [8].

If tumor growth is chaotic, this could explain the unreliability of treatment and prediction of tumor evolution. More importantly, if chaos is established, this could be used to adjust strategies for fighting cancer using chaos control and/or anti-control [9].

In this paper, a plausible chaotic diffusion model of tumor growth and decay is presented, as a combination of theoretical modelling and empirical search.

II. A REACTION–DIFFUSION CANCER GROWTH MODEL

Recently, a multiscale diffusion cancer-invasion model (MDCM) was presented in [9], [10], [11], [12], [13], [14], [15], [16], [17], which considers cellular and microenvironmental factors simultaneously and interactively. The model was classified as hybrid, since a continuum deterministic model (based on a system of reaction–diffusion chemotaxis equations) controls the chemical and extracellular matrix (ECM) kinetics and a discrete cellular automata-like model (based on a biased random-walk model) controls the cell migration and interaction. The interactions of the tumor cells, matrix–metalloproteinases (MMs), matrix-degradative enzymes (MDEs) and oxygen are described by the four coupled rate PDEs:

\[
\begin{align*}
\frac{\partial n}{\partial t} &= D_n \nabla^2 n - \chi \nabla \cdot (n \nabla f), \\
\frac{\partial f}{\partial t} &= -\delta m f, \\
\frac{\partial m}{\partial t} &= D_m \nabla^2 m + \mu n - \lambda m, \\
\frac{\partial c}{\partial t} &= D_c \nabla^2 c + \beta f - \gamma n - \alpha c,
\end{align*}
\]

where \(n\) denotes the tumor cell density, \(f\) is the MM–concentration, \(m\) corresponds to the MDE–concentration, and \(c\) denotes the oxygen concentration. The four variables, \(n, m, f, c\), are all functions of the 3-dimensional spatial variable \(x\) and time \(t\). All equations represent diffusion except (2), which shows only temporal evolution of the MM–concentration coupled to the MDE–concentration. \(D_n\) is the tumor cell coefficient, \(D_m\) is the MDE coefficient and \(D_c > 0\).

1The chaotic behavior of a system may be artificially weakened or suppressed if it is undesirable. This concept is known as control of chaos. The first and the most important method of chaos control is the so–called OGY–method, developed by [10]. However, in recent years, a non-traditional concept of anti-control of chaos has emerged. Here, the non-chaotic dynamical system is transformed into a chaotic one by small controlled perturbation so that useful properties of a chaotic system can be utilized [20], [21].
is the oxygen diffusion coefficient, while \( \chi, \mu, \lambda, \delta, \alpha, \gamma, \beta \) are positive constants. The other terms respectively denote: 

- \( \chi \nabla \cdot (n \nabla f) \) — haptotaxis;
- \( \mu N \) — production of MDE by tumor cell;
- \( \lambda m \) — decay of MDE;
- \( \alpha c \) — natural decay of oxygen;
- \( \gamma n \) — oxygen uptake; and
- \( \beta f \) — production of oxygen by MM.

Because of its hybrid nature (cells treated as discrete entities and microenvironmental parameters treated as continuous concentrations), the 4-dimensional (4D) model \((1)–(4)\) can be directly linked to experimental measurements of those cellular and microenvironmental parameters recognized by cancer biologists as important in cancer invasion. Furthermore, the fundamental unit of the model is the cell, and the complex collective behavior of the tumor emerges as a consequence of interactions between factors influencing the life cycle and movement of individual cells \([9], [11], [12], [15], [16], [17]\).

In order to use realistic parameter values, the system of rate equations \((1)–(4)\) was non-dimensionalised. The resulting 4D scaled system of rate PDEs \((11)\) is given by

\[
\begin{align*}
\frac{\partial n}{\partial t} &= d_n \nabla^2 n - \rho \nabla \cdot (n \nabla f), \\
\frac{\partial f}{\partial t} &= -\eta m f, \\
\frac{\partial m}{\partial t} &= d_m \nabla^2 m + \kappa n - \sigma m, \\
\frac{\partial c}{\partial t} &= d_c \nabla^2 c + \nu f - \omega n - \phi c.
\end{align*}
\]

In \((11)\) the values of the non-dimensional parameters were given as:

\[
d_n = 0.0005, \quad d_m = 0.0005, \quad d_c = 0.5, \quad \rho = 0.01, \quad \eta = 50, \quad \kappa = 1, \quad \sigma = 0, \quad \nu = 0.5, \quad \omega = 0.57, \quad \phi = 0.025.
\]

The 4D hybrid PDE–model \((1)–(4)\) can be seen as a special case of a general multi-phase tumor growth PDE \((2)\) equation \((12)\),

\[
\frac{\partial \Phi_i}{\partial t} + \nabla \cdot (\nu_i \Phi_i) = \nabla \cdot (D_i \Phi_i) + \lambda_i(\Phi_i, C_i) - \mu_i(\Phi_i, C_i),
\]

where for phase \(i\), \( \Phi_i \) is the volume fraction \( \sum_i \Phi_i = 1 \), \( \nu_i \) is the velocity, \( D_i \) is the random motility or diffusion, \( \lambda_i(\Phi_i, C_i) \) is the chemical and phase dependent production, and \( \mu_i(\Phi_i, C_i) \) is the chemical and phase dependent degradation/death. The multi-phase model \((10)\) has been derived from the basic conservation equations for the different chemical species,

\[
\frac{\partial C_i}{\partial t} + \nabla \cdot \mathbf{N}_i = P_i,
\]

where \( C_i \) are the concentrations of the chemical species, subindex \( a \) for oxygen, \( b \) for glucose, \( c \) for lactate ion, \( d \) for carbon dioxide, \( e \) for bicarbonate ion, \( f \) for chloride ion, and \( g \) for hydrogen ion concentration; \( \mathbf{N}_i \) is the flux of each of the chemical species inside the tumor spheroid; and \( P_i \) is the net rate of consumption/production of the chemical species both by tumor cells and due to the chemical reactions with other species.

In this paper we will search for a temporal 3D cancer chaotic attractor ‘buried’ within the 4D hybrid spatio-temporal model \((1)–(4)\).

### III. A CHAOTIC MULTI-SCALE CANCER GROWTH/DEATH MODEL

From the non-dimensional spatio-temporal AC model \((5)–(8)\), discretization was performed by neglecting all the spatial derivatives resulting in the following simple 4D temporal dynamical system.

\[
\begin{align*}
\dot{n} &= 0, \\
\dot{f} &= \alpha \eta (m - f), \\
\dot{m} &= \kappa n - \sigma m, \\
\dot{c} &= \nu f - \omega n - \phi c.
\end{align*}
\]

When simulated, the temporal system \((11)–(14)\) with the set of parameters \((9)\) exhibits a virtually linear temporal behavior with almost no coupling between the four concentrations that have very different quantitative values (all phase plots between the four concentrations, not shown here, are virtually one-dimensional). To see if a modified version of the system \((11)–(14)\) could lead to a chaotic description of tumor growth, four new parameters, \( \alpha, \beta, \gamma, \) and \( \delta \) were introduced. The resulting model is

\[
\begin{align*}
\dot{n} &= 0, \\
\dot{f} &= \alpha \eta (m - f), \\
\dot{m} &= \kappa n - \sigma m, \\
\dot{c} &= \nu f - \omega n - \phi c.
\end{align*}
\]

The introduction of the parameters \((\alpha, \beta, \gamma, \delta)\) was motivated by the fact that tumor cell shape represents a visual manifestation of an underlying balance of forces and chemical reactions \([32]\). Specifically, the parameters represent the following quantities:

- \( \alpha \) — tumor cell volume (proliferation/non-proliferation fraction),
- \( \beta \) — glucose level,
- \( \gamma \) — number of tumor cells,
- \( \delta \) — diffusion from the surface (saturation level).

A tumor is composed of proliferating \( (P) \) and quiescent (or non-proliferating) \( (Q) \) cells. Tumor cells shift from class \( P \) to class \( Q \) as the tumor grows in size \([33]\). Model dependence on the ratio of proliferation to non-proliferation is introduced via the first parameter, \( \alpha \). The discretization of equation \((5)\) leads to cell density being modelled as a constant in equation \((11)\). Accordingly, cell density does not play a role in the dynamics. In \((15)–(18)\) the cell density is re-introduced into the dynamics via the cell number, \( \gamma \). The importance of introducing \( \gamma \) also appears in connection with the cyclin-dependent kinase (Cdk) inhibitor p27, the level and activity of which increase in response to cell density. Levels and activity of Cdk inhibitor p27 also increase with differentiation following loss of adhesion to the ECM \([29]\).

The ability to estimate the growth pattern of an individual tumor cell type on the basis of morphological measurements should have general applicability in cellular investigations,
cell–growth kinetics, cell transformation and morphogenesis [34].

Cell spreading alone is conducive to proliferation and increases in DNA synthesis, indicating that cell morphology is a critical determinant of cell function, at least in the presence of optimal growth factors and extracellular matrix (ECM) binding [55]. In many cells, the changes in morphology can stimulate cell proliferation through integrin-mediated signaling, indicating that cell shape may govern how individual cells will respond to chemical signals [36].

Parameters \((\alpha, \beta, \gamma, \delta)\), introduced in connection with can-

The new tumor–growth model \((19)–(22)\) retains all the qualities of the original AC model \((5)–(8)\) plus includes the temporal chaotic ‘butterfly’–attractor. This chaotic behavior may be a more realistic view on the tumor growth, including stochastic–like long–term unpredictability and uncontrollability, as well as sensitive dependence of a tumor growth on its initial conditions.

Based on the new tumor growth model \((19)–(22)\), we have re-formulated the following generic concept of carcinogenesis and metastasis (see scheme on the following page). With the model of strongly coupled PDEs, remodelling of extracellular matrix (ECM) causes a whole process of the movement of invading cells with increased haptotaxis, and at the same time decreased enzyme productions level. This can alter chromatin structure, which plays an important role in initiating, propagating and terminating cellular response to DNA damage [28].

The effect of haptotaxis in the process of cells invading could be modelled with travelling-wave (Fisher) equation \([18]\).

The proposed model \((19)–(22)\) describes chaotic behavior relevant to the invasion of cancer cells. As devices for controlling metastasis/chaos we suggest the following processes: Cellular retraining of cancer stem cells and/or activation of positive function of cyclin-dependent kinase inhibitor p27 and/or decreased expression of SATB1, which is correlated with aggressive tumor phenotype in breast cancer and shorter patient survival time [27], [29], [30], [31]. To connect the new parameters \((\alpha, \beta, \gamma, \delta)\) to the therapeutic regime we note the fact that significant factor of any therapy is tumor re-growth during the rest periods between therapy applications, which is again dependent on proliferation fraction dynamics \(\alpha\) [33].

Also, the age of the tumor may translate to different levels of response to a standard therapy. As mentioned earlier, the number of cells, \(\gamma\), is connected with the Cdk inhibitor p27, for which levels and activity increase in response with the cell density \(\gamma\), differentiation following loss of adhesion to the ECM. Cdk inhibitor p27 regulates cell proliferation, cell motility and apoptosis and is the essential element for understanding transduction pathways in the regulation of normal and malignant cell proliferation as well as it is new hope for therapeutic intervention [29].

Introducing the parameter set \((\alpha, \beta, \gamma, \delta)\) into the model of tumor cell morphology and function could lead to insight into the relationship between these parameters and chromatin. By varying these parameters, it may be possible to predict situations that result in dangerous levels of chromatin. High levels of chromatin are associated with cancer metastasis and some of the most aggressive cancer types [30], [31].

The new temporal model \((15)–(18)\) (as well as the corre-

IV. A CHAOTIC REACTION–DIFFUSION CANCER GROWTH/DECAY MODEL

The spatio-temporal system of rate PDEs corresponding to the system in \((15)–(18)\) provides the following multi-scale cancer invasion model.

\[
\begin{align*}
\frac{\partial m}{\partial t} &= d_m \nabla^2 m + \alpha f - \beta m - \gamma c - \delta m, \quad \text{(19)} \\
\frac{\partial f}{\partial t} &= \alpha \eta (m - f), \quad \text{(20)} \\
\frac{\partial m}{\partial t} &= d_m \nabla^2 m + \alpha f - \beta m - \gamma c - \delta m, \quad \text{(21)} \\
\frac{\partial c}{\partial t} &= d_c \nabla^2 c + \nu f - \omega n - \phi c. \quad \text{(22)}
\end{align*}
\]

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Fig. 1. A 3D Lorenz-like chaotic attractor (see [22], [23]) from the modified tumor growth model \((15)-(18)\). The attractor effectively couples the MM–concentration \(n\), the MDE–concentration \(m\), and the oxygen concentration \(c\) in a mask–like fashion.

Parameters \((\alpha, \beta, \gamma, \delta)\), introduced in connection with cancer cells morphology and dynamics could also influence the very important factor chromatin associated with aggressive tumor phenotype and shorter patient survival time. For computations, the parameters were set to \(\alpha = 0.06, \beta = 0.05, \gamma = 26.5\) and \(\delta = 40\). Small variation of these chosen values would not affect the qualitative behavior of the new temporal model \((15)–(18)\). Simulations of \((15)–(18)\), using the same initial conditions and the same non-dimensional parameters as before, show chaotic behavior in the form of Lorenz-like strange attractor in the 3D \((f - m - c)\) subspace of the full 4D \((n - f - m - c)\) phase-space (see Figure 1).
not sensitive to variation of the \((\alpha, \beta, \gamma, \delta)\) values, but is sensitive to their corresponding places in the equations.

V. Conclusion

A plausible chaotic multi-scale cancer-invasion and decay model has been presented. The new model was formulated by introducing nonlinear coupling into the existing hybrid multiscale Anderson-Chaplain model. The new model describes chaotic behavior, as well as sensitivity dependence of a tumor evolution on its initial conditions. Effective cancer control is reflected in progressive reduction in cancer mortality [27]. The proposed model suggests a possible solution to carcinogenesis and metastasis, by combining mathematical modelling with latest medical discoveries.

REFERENCES

[1] R.A. Gatenby, P.K. Maini, Mathematical oncology: Cancer summed up. Nature, 421, 321, (2003)
[2] T. Roose, S.J. Chapman, P.K. Maini, Mathematical Models of Avascular Tumor Growth. SIAM Rev. 49(2), 179–208, (2007).
[3] V. Ivancevic, T. Ivancevic, Geometrical Dynamics of Complex Systems. Springer, Dordrecht, (2006)
[4] V. Ivancevic, T. Ivancevic, Complex Dynamics: Advanced System Dynamics in Complex Variables. Springer, Dordrecht, (2007)
[5] T. Ivancevic, L. Jain, J. Pattison, A. Hariz, Nonlinear Dynamics and Chaos Methods in Neurodynamics and Complex Data Analysis. Nonl. Dyn. (Springer) (to appear)
[6] G. Giurini, E. Onofri, E. Menghetti, New horizons in medicine. The attractors. Recenti Prog. Med. (in Italian) 84(9), 618-623, (1993).
[7] R. Sedivy, Fractal tumours: their real and virtual images. Wien Klin. Wochenschr. (in German) 108(17), 547-551, (1996).
[8] R. Sedivy, C. Windischberger, Fractal analysis of a breast carcinoma—presentation of a modern morphometric method. Wien Klin. Wochenschr. (in German) 148(1/2), 335-337, (1998).
[9] A.R.A. Anderson, M.A.J. Chaplain, Continuous and discrete mathematical models of tumor-induced angiogenesis. Bul. Math. Biol. 60, 857-900, (1998).
[10] A.R.A. Anderson, M.A.J. Chaplain, E.L. Newman, R.J.C. Steele, A.M. Thompson, Mathematical modelling of tumour invasion and metastasis. J. Theor. Med. 2, 129-154, (2000).
[11] A.R.A. Anderson, A hybrid mathematical model of solid tumour invasion: The importance of cell adhesion. Math. Med. Biol. 22, 163–186, (2005).
[12] A.R.A. Anderson, A.M. Weaver, P.T. Cummings, V. Quaranta, Tumor Morphology and Phenotypic Evolution Driven by Selective Pressure from the Microenvironment. Cell 127, 905–915, (2006).
[13] M.A.J. Chaplain, S.R. Mc Dougal, A.R.A. Anderson, Mathematical modelling of tumor-induced angiogenesis. Ann. Rev. Biomed. Eng. 8, 233-257, (2006).
[14] H. Enderling, A.R.A. Anderson, M.A.J. Chaplain, Visualisation of the numerical solution of partial differential equation systems in three space dimensions and its importance for mathematical models in biology. Math. Biosci. 3(4), 571-582, (2006).
[15] H. Enderling, M.A.J. Chaplain, A.R.A. Anderson, J.S. Vaidya, A mathematical model of breast cancer development, local treatment and recurrence. J. Th. Biol. 246, 245259, (2007).
[16] I. Ramis-Conde, M.A.J. Chaplain, A.R.A. Anderson, Mathematical modelling of cancer cell invasion of tissue. Math. Comp. Mod. 47, 533-545, (2008).
[17] A. Gerish, M.A.J. Chaplain, Mathematical modelling of cancer cell invasion of tissue: Local and non-local models and the effect of adhesion. J. Th. Biol. 250, 684–704, (2008).
[18] B.P. Marchant, J. Norbury, J.A. Sherratt, Travelling wave solutions to a haptotaxis-dominated model of malignant invasion. Nonlinearity, 14, 16531671, (2001).
[19] E. Ott, C. Grebogi, J.A. Yorke, Controlling chaos. Phys. Rev. Lett., 64, 1196–1199, (1990).
[20] V. Ivancevic, T. Ivancevic, High-Dimensional Chaotic and Attractor Systems. Springer, Berlin, (2006).
[21] V. Ivancevic, T. Ivancevic, Complex Nonlinearity: Chaos, Phase Transitions, Topology Change and Path Integrals, Springer, Series: Understanding Complex Systems, Berlin, (in press).
[22] E.N. Lorenz, Deterministic Nonperiodic Flow. J. Atmos. Sci., 20, 130–141, (1963).
[23] C. Sparrow, The Lorenz Equations: Bifurcations, Chaos and Strange Attractors. Springer, New York, (1982).
[24] V. Ivancevic, T. Ivancevic, Neuro-Fuzzy Associative Machinery for Comprehensive Brain and Cognition Modelling. Springer, Berlin, (2007)
[25] V. Ivancevic, T. Ivancevic, Computational Mind: A Complex Dynamics Perspective. Springer, Berlin, (2007).
[26] J.P. Sleeman, N. Cremers, New concepts in breast cancer metastasis: tumor initiating cells and the microenvironment. Clin. Exp. Metastasis. 24(8), 707–15, (2007).
[27] I.P. Janecka, Cancer control through principles of systems science, complexity, and chaos theory: A model. Int. J. Med. Sci. 4(3), 164-173, (2007).
[28] J.A. Downs, M.C. Nussenzweig, A. Nussenzweig, Chromatin dynamics and the preservation of genetic information. Nature, 447, 951-958, 21 June 2007.
[29] I.M. Chu, L. Hengst, J.M. Slingerland, The Cdk inhibitor p27 in human cancer: prognostic potential and relevance to anticancer therapy. Nature Rev. Cancer, 8, 253-287, April 2008.
[30] S. Cai, C.C. Lee, T. Kohwi-Shigematsu, SATB1 packages densely looped, transcriptionally active chromatin for coordinated expression of cytokine genes. Nature Genet. 38, 1278-1288, (2006).
[31] H.-J. Han, J. Russo, Y. Kohwi, T. Kohwi-Shigematsu, SATB1 programs gene expression to promote breast tumor growth and metastasis. Nature, 452, 187-193, (2008).
[32] Olive, P.L., Durand, R.E., Drug and radiation resistance in spheroids: cell contact and kinetics. Cancer Metastasis Rev. 13, 121, (1994).
[33] Koziusko, F., Bourdeau, M., A unified model of sigmoid tumour growth based on cell proliferation and quiescence, Cell Prolif. 40(6), 824-834, (2007).
[34] Castro, M.A.A., Klamt, F., Grieneisen, V.A., Grivicich, I., Moreira, J.C.F., Gompertzian growth pattern correlated with phenotypic organization of colon carcinoma, malignant glioma and non-small cell lung carcinoma cell lines. Cell Prolif. 36(2), 65-73, (2003).
[35] Ingber, D.E., Fibronectin controls capillary endothelial cell growth by modulating cell shape. Proc. Natl. Acad. Sci. USA 87, 3579, (1990).
[36] Boudreau, N., Jones, P.L., Extracellular matrix and integrin signaling: the shape of things to come. Biochem. J. 339, 481, (1999).