



FERROPTOSIS AS A BIOLOGICAL PHASE TRANSITION I: AVASCULAR AND VASCULAR TUMOR GROWTH

J. M. Nieto-Villar^{1*} and R. Mansilla²

¹Department of Chemical-Physics, A. Alzola Group of Thermodynamics of Complex Systems of M.V. Lomonosov Chair, Faculty of Chemistry, University of Havana, Cuba.

²Centro de Investigaciones Interdisciplinarias en Ciencias y Humanidades, UNAM, México.

***Corresponding Author: J. M. Nieto-Villar**

Department of Chemical-Physics, A. Alzola Group of Thermodynamics of Complex Systems of M.V. Lomonosov Chair, Faculty of Chemistry, University of Havana, Cuba.

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ABSTRACT

Herewith we discuss a network model of the ferroptosis avascular and vascular tumor growth based on our previous proposed framework. Chiefly, ferroptosis should be viewed as a “first order” phase transition characterized by a supercritical Andronov–Hopf bifurcation, with the emergence of limit cycle. The increase of the population of the oxidized PUFA fragments, take as the control parameter, involves an inverse Feigenbaum, (a cascade of saddle-foci Shilnikov’s bifurcations) scenario, which results in the stabilization of the dynamics and in a decrease of complexity.

KEYWORDS: Biological phase transition; Ferroptosis cancer; avascular and vascular tumor growth; Shilnikov’s chaos.

1. INTRODUCTION

According to the WHO [World Health Organization] cancer is the second leading cause of death worldwide, and it is estimated that the number of new cases will increase in the coming years.

There is enough evidence [Gottesman *et al.*, 2016; Bizzarri, *et al.*, 2011] regarding the complexity of cancer. We mean that cancer can be seen as a self-organizing nonlinear dynamic system, far from thermodynamic equilibrium [Deisboeck *et al.*, 2001; Rockmore, 2005; Izquierdo-Kulich & Nieto-Villar, 2013], exhibits a fractal structure that allows it to evade the action of the immune system and host cells [Bru, *et al.*, 2003; Kitano, 2004; Llanos-Perez *et al.*, 2015; Betancourt-Mar *et al.*, 2017]. The growth dynamics exhibit a deterministic chaos type, which confers high robustness, poor long-term prognosis, adaptability, and learning capacity [Itik, S. P. Banks, 2010; El-Gohary, 2008; Llanos-Perez *et al.*, 2016].

As we have shown in previous works [Montero *et al.*, 2018; Guerra, *et al.*, 2018; Betancourt-Mar *et al.*, 2017; Llanos-Perez *et al.*, 2015], cancer can be seen as a complex network made up of cells that have lost their specialization and growth control, and that emerges through what we can call “biological phase transition” [Montero *et al.*, 2018]. Indeed, even subtle changes in some critical values may impair the self-organization process, leading to unexpected different states, exhibiting

variable robustness and adaptability capability within the attractor landscape [Montero *et al.*, 2018].

Overall, the development of a primary tumor from a microscopic level (avascular growth) to a macroscopic level (vascular phase), and the subsequent appearance of metastases, is not simply the accumulation of malignant cells, but results from a nonlinear process involving true “biological phase transition” downstream critical bifurcations [Betancourt-Mar *et al.*, 2017; Martin, *et al.*, 2017]. This dynamical behavior leads to self-organization away from thermodynamic equilibrium, providing the system with a high degree of robustness, complexity, and hierarchy [Montero *et al.*, 2018], which, in turn, enacts the creation of new information and learning ability.

Many of the cancer therapies such as chemotherapy and radiotherapy are not specific, they have marked side effects. As a fact, it is well known that only 60% of different types of cancers can be healed through with the conventional therapies, they are also accompanied by undesirable side effects [Schulz, 2005].

Ferroptosis is a type of iron-dependent programmed cell death, characterized by the accumulation of free radicals and reactive oxygen species (ROS), such as, lipid peroxides, radicalsuperoxide, hydroxyl radical, hydrogen peroxide and so on; and is genetically and biochemically distinct from other forms of regulated cell death such as

apoptosis [Dixon *et al.*, 2012].

Three essential hallmarks define ferroptosis [Dixon & Stockwell, 2019], namely: The loss of lipid peroxide repair capacity by the phospholipid hydroperoxidase GPX4, the availability of redox- active iron and oxidation of polyunsaturated fatty acid (PUFA) containing phospholipids.

An open question is whether any type of lethal lipid peroxidation is classified as ferroptosis or whether only certain types of lethal lipid peroxidation should be termed ferroptosis [Feng & Stockwell, 2018]. In fact, the way lipid peroxidation leads to ferroptosis remains an unsolved mystery [Feng & Stockwell, 2018]. On one hand, exist the evidence that ferroptosis processes are associate to the pathogenesis of several degenerative diseases such as, cardiovascular disorders, cancer, atherosclerosis, diabetes, Alzheimer dementia (SDAT), just to mention the most relevant [Hong-fa Yan *et al.*, 2021; Ames *et al.*, 1993]. It leads to progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death [Stockwell, *et al.*, 2017; Liochev, 2013; Harman, 2006].

On the other hand, numerous studies have demonstrated the effectiveness of cancer-killing by inducing ferroptosis, which is mainly accomplished by elevating the intracellular ROS levels and inactivating the activity of GPX4 [Shen, *et al.*, 2018; Shimada, *et al.*, 2016; Kim, *et al.*, 2016].

To the best of our knowledge, only a few models related to ferroptosis have been reported [Kagan, *et al.*, 2017; Agmon, *et al.*, 2018; Konstorum, 2020]. Kagan *et al.* [Kagan, *et al.*, 2017] developing a continuum model for ferroptosis with a focus on biochemical cascades. While that model provides an excellent synthesis of specific processes involved, it excludes contributions of the lipid peroxidation processes involved in ferroptosis. Agmon *et al.* [Agmon, *et al.*, 2018] performed molecular dynamics simulations of membranes with compositions relevant to ferroptotic sensitivity, and showed how the biophysical properties of membranes are altered under ferroptotic-competent lipid compositions. Most recently, Konstorum [Konstorum, 2020] has develop a multistate discrete modeling approach to emphasize qualitative properties of signaling cascades relevant to ferroptosis. The discrete modeling approach allows to explore the relative importance of different drivers of ferroptosis using a wider range of data than would be available for a detailed kinetic model of the system. As far as the authors know, there is no model that connects the lipid peroxidation processes involved in ferroptosis with the growth of cancer cells.

The main goal of the present work is establishing a heuristic model that connects lipid peroxidation, the evolution of the carcinogenic cells in the avascular and vascular phases [Roose, *et al.*, 2007] and the ferroptosis

process. The model contains three populations species: $r(t)$ -lipid peroxides, $x(t)$ -avascular tumor cells and $y(t)$ -vascular tumor cells.

The manuscript is organized as follows: in Section 2 we propose a network model for the ferroptosis avascular and vascular tumor growth. Section 3 focuses into the analysis of the mathematical model derived from the mechanism previously proposed, including quantitative simulations and stability analyze. The development of a thermodynamic framework based on the entropy production rate is presented in Section 4. Finally, some concluding remarks are presented.

2. A network model of the ferroptosis

There is enough evidence and consensus in the literature related to ferroptosis-mediated anticancer effects [Wang, *et al.*, 2019; Dierge *et al.*, 2021; Hassannia, *et al.*, 2019]. However, the mechanisms underlying each step of this complex process remains unclear [Xu, *et al.*, 2019; Agmon, *et al.*, 2018; Feng & Stockwell, 2018]. Fig. 1 shows the network structure of the model proposed by us, where a connection is established between lipid peroxidation, the evolution of cancer in the avascular and vascular phases, respectively, and the ferroptosis processes.

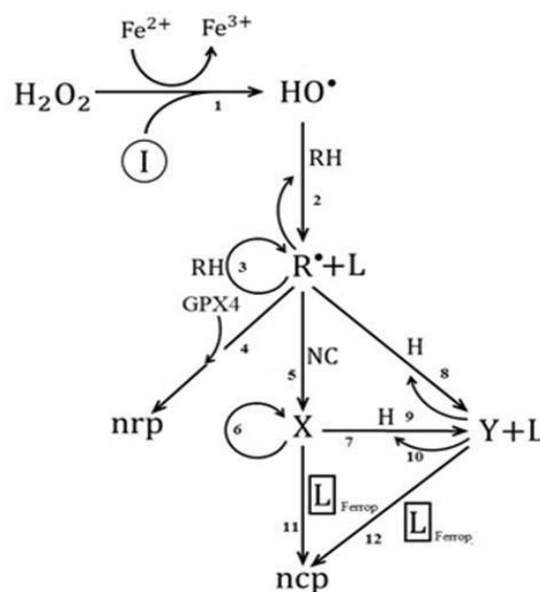


Fig. 1: The network model of ferroptosis avascular and vascular tumor growth.

In the network model, the symbol I represents the ferroptosis-inducing agents, such as iron-based nanomaterials, for example ferumoxytol, amorphous iron nanoparticles iron-organic frameworks, ionizing radiation-induced, and so on [Wang, *et al.*, 2019; Zhang, *et al.*, 2020]; H_2O_2 is a hydrogen peroxide; $HO^\bullet$ are the hydroxyl radicals; RH represents the polyunsaturated fatty acids (PUFAs); NC are the population of normal cells exposed to the pro-carcinogenic stimulus; H the population of the host cells in the surrounding environment [Brú, *et al.*, 2003], comprising exclusively

epithelial cells; GPX4 glutathione peroxidase 4; L represents the population of the oxidized PUFA fragments [Agmon, *et al.*, 2018].

In this sense, we conjecture that L encourages the ferroptosis of cancer cells. For this reason we take $[L]_{CP}$ as the control parameter (CP).

Variables species: r, x, y represent: $r(t)$ the population of lipid peroxides species, $x(t)$, $y(t)$, the population of tumor cells in the avascular and vascular state, respectively. Finally, n_{rp} and n_{cp} represents a non-radical products and non-cancerous products respectively.

Step 1 is associated with the Fenton reaction [Cheng & Li, 2007], step 2 is related to formation of the Lipid peroxides [Bebber, 2020], step 3 is the propagate lipid peroxidation chain reactions [Spiteller & Afzal, 2014], step 4 is the primary cellular mechanism of protection against reactive oxygen species (ROS), which is mediated by glutathione peroxidase 4 (GPX4) [Dreger, *et al.*, 2009], steps 5, 6 and 7, 10 are related to the process of mitosis and apoptosis of the proliferating tumor cells respectively; steps 8 and 9 correspond to the action of the host H [Brú, *et al.*, 2003], finally, steps 11 and 12 are related to the ferroptosis avascular and vascular tumor growth.

The constants and concentration of species for the model proposed (see Fig. 1) were chosen empirically, dimensionless and trying to have a greater generality and simplicity as possible, so we have: $k_1 = 1$, $k_2 = 4$, $k_3 = 2$, $k_4 = 0.1$, $k_5 = 0.5$, $k_6 = 4$, $k_7 = 0.1$, $k_8 = 1$, $k_9 =$

0.5 , $k_{10} = 0.001$, $k_{11} = k_{12} = 1$. $[RH] = 5$, $[GPX4] = 0.01$, $[H] = 3$, $[HO^*] = -0.001$, $[NC] = 1$, $[L]_{CP} = [4-0.3]$.

3. Mathematical model, stability analysis and numerical simulations

Mathematical models represent a suitable way for formalizing the knowledge of living systems obtained through a Systems Biology approach [Montero *et al.*, 2018]. Mathematical modeling of tumor growth makes possible the description of its most important regularities and it is useful in providing effective guidelines for cancer therapy, drug development, and clinical decision-making [Preziosi, 2003; Araujo & McElwain, 2004; Bellomo, *et al.*, 2008].

Although the role of the ferroptosis-mediated anticancer effects is well documented in literature, [Dierge *et al.*, 2021] there are just few reports dealing with the ferroptosis dynamics [Kagan, *et al.*, 2017; Agmon, *et al.*, 2018; Konstorum, 2020]. Indeed, most of the computational dynamic of ferroptosis focus on the genetic and biophysical changes associated.

The network model we propose (Fig. 1) is a qualitative representation of the ferroptosis avascular and vascular tumor growth, based on the experimental evidences already available. In agreement with that model (Fig. 1) and the law of mass action governing chemical kinetics, a system of ordinary differential equations ODEs (1) was obtained, which describes the ferroptosis avascular and vascular tumor growth.

$$\begin{aligned}\frac{dr}{dt} &= (a_1 - a_2 y + a_3) r - (a_4 + a_5) r^2 \\ \frac{dx}{dt} &= a_6 r^2 + (k_6 - k_{11} L) x - 2k_7 x^2 - a_7 xy + k_{10} y^2 \\ \frac{dy}{dt} &= -k_{12} L y + k_7 x^2 + a_7 xy - 2k_{10} y^2\end{aligned}\quad (3.1)$$

where,

$$\begin{aligned}a_1 &= k_3 (RH), a_2 = k_8 (H), a_3 = k_2 (RH)(HO^*), a_4 = 2k_5 (NC), a_5 = 2k_4 (GPX4), \\ a_6 &= k_5 (NC), a_7 = k_9 (H).\end{aligned}$$

Fixed points, stability analysis and bifurcations were calculated using the standard procedure [Andronov & Khaikin, 1949; Anishchenko, *et al.*, 2003; Kuznetsov, 2013]. The control parameter (CP) were represented the population of the oxidized PUFA fragments $[L]_{CP}$ [Agmon, *et al.*, 2018]. Sensitivity analysis were done [Varma & Morbidelli, 2005] and quantitative investigation of the behavior of the output variables as the parameters of the system change.

The Lyapunov exponents were calculated using the Wolf

algorithm in Fortran language [Wolf, *et al.*, 1985]. Lyapunov dimension D_L , Eq. (2) also known as Kaplan-Yorke dimension [Frederickson, *et al.*, 1983], was evaluated across the spectrum of Lyapunov exponents λ_j as:

$$D_L = j + \frac{\sum_{i=1}^j \lambda_i}{|\lambda_{j+1}|} \quad (3.2)$$

where j is the largest integer number for which $\lambda_1 + \lambda_2 + \dots + \lambda_j \geq 0$.

For simulation the network model, COPASI v.4.22.170 software was used. However, numerical integration was performed on the system of ODEs Eq. (3.1) through

implementation of Gear algorithm for stiff equations, in Fortran with double precision and tolerance of 10^{-8} [Gear, 1968]. In Table 1 we show the dynamical behavior of the proposed ODEs (3.1) for different values of the control parameter [L]CP.

Table 1: Stability, and complexity for the system of ODEs (3.1) for different values of the control parameter [L]_{CP} = [4-0.3].

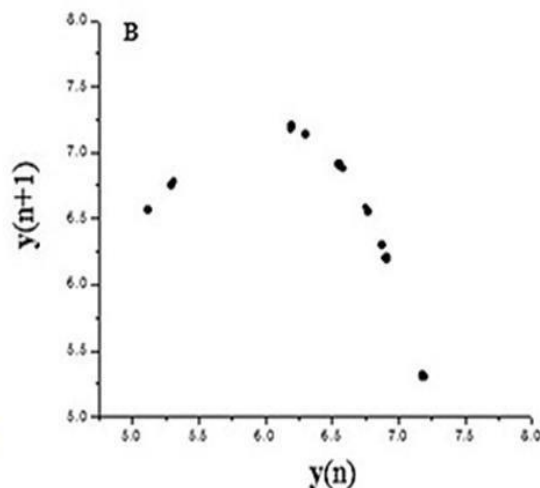
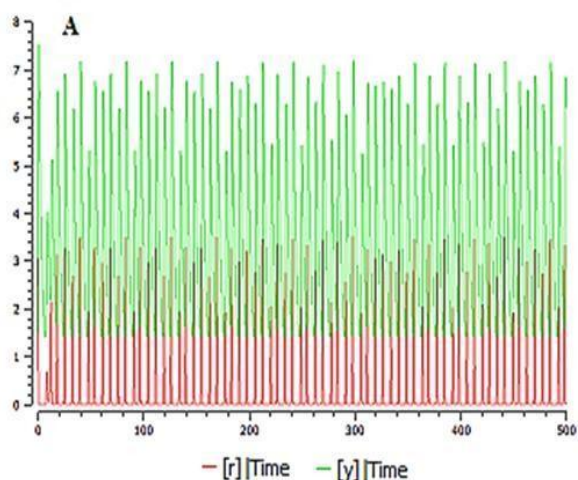
L	Eigenvalues of the Jacobian matrix $\mathcal{E}_i$	Lyapunov exponents λ_j	Lyapunov dimension D_L
4ss _s stable focus	$\mathcal{E}_{1,2} = -0.158 \pm 5.37i, \mathcal{E}_3 = -8.050$	$\lambda_1 = -0.157,$ $\lambda_2 = -0.159,$ $\lambda_3 = -8.048$	0
3 Limit cycle	$\mathcal{E}_{1,2} = 0.083 \pm 4.80i, \mathcal{E}_3 = -6.719$	$\lambda_1 = 0.00,$ $\lambda_2 = -0.15,$ $\lambda_3 = -6.626$	1
0.57 P2 (2-period)	$\mathcal{E}_{1,2} = 0.273 \pm 2.29i, \mathcal{E}_3 = -2.761$	$\lambda_1 = 0.00,$ $\lambda_2 = 0.00,$ $\lambda_3 = -1.957$	2
0.42 P4 (4-period)	$\mathcal{E}_{1,2} = 0.249 \pm 2.01i, \mathcal{E}_3 = -2.439$	$\lambda_1 = 0.00,$ $\lambda_2 = 0.00,$ $\lambda_3 = -1.718$	2
0.3 Shilnikov's chaos	$\mathcal{E}_{1,2} = 0.220 \pm 1.73i, \mathcal{E}_3 = -2.156$	$\lambda_1 = 0.044,$ $\lambda_2 = 0.00,$ $\lambda_3 = -1.587$	2.102

In Fig. 2, the dynamic behavior of the network model is shown. It is observed as for low values of the control parameter ($L = 0.3$), the tumor cells exhibit “apparently random behavior” (remnant of Shilnikov's chaos), (see Table 1) [Shilnikov, *et al.*, 2001] (Fig. 2 A, B, C) with a predominance of the population of vascular tumor cells y (t) (green). This behavior has important biological implications. On the one hand, the high sensitivity of the system to initial conditions makes unfeasible long-term predictions, i.e. the end forecasts are improbable (poor prognosis).

Furthermore, the system displays a high degree of complexity [Betancourt-Mar & Nieto-Villar, 2007;

Kitano, 2003]. This implies cancer cells are resilient in respect to pharmacological treatment, thus leading to a low response rate [Kim, *et al.*, 2015].

As can be seen (see Fig. 2D) the increase of the population of the oxidized PUFA fragments, take as the control parameter L , produces an inverse Feigenbaum, (a cascade of saddle-foci Shilnikov's bifurcations) scenario, which results in the stabilization of the dynamics and in a decrease complexity of the system.



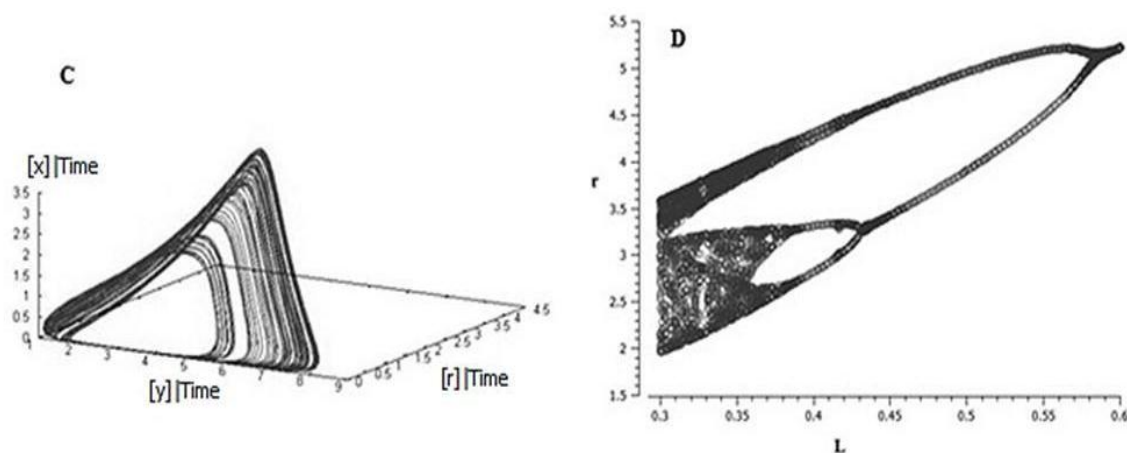


Fig. 2: Ferroptosis tumor growth dynamics for the proposed model (3.1), the control parameter values ($L = 0.3$): the population of lipid peroxides species r (red) and y (green) are the population vascular tumor cells; A. time series; B. Iterated unimodal map obtained from plotting successive local maxima of the time dynamics of vascular y (green) tumor cells; C. Chaotic attractor; D. Bifurcation diagram obtained from $r_{\max}$ showing the period-halving (i.e. inverse Feigenbaum) scenario occurring as the inactivation of the population of the oxidized PUFA fragments L by tumor cells decreases. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

As matter of the fact, at the critical point $L = 3.383$, a supercritical Andronov–Hopf bifurcation takes place (Kuznetsov), and at $L = 4$, giving rise to a stationary state. Furthermore, the sensitivity analysis of the model showed that the fundamental processes in decreasing order of their importance in the steady state ($L = 4$, ss_s) are the following: 3, 12, 11, 8 and 9. This shows how the

propagation process of peroxidation lipid (3) and ferroptosis in avascular and vascular growth (12,11) have a pivotal position in our model.

Figure 3 shows the dynamic behavior for different values of the control parameter L .

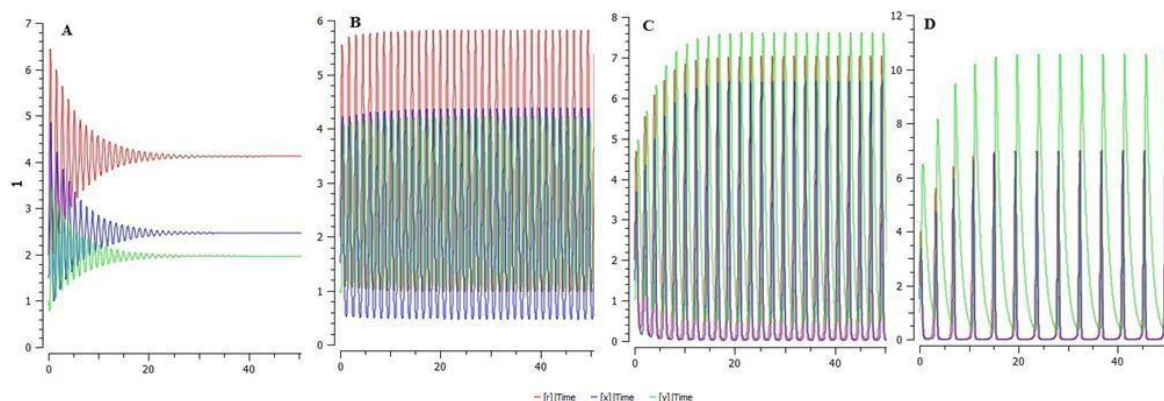


Fig. 3 Time series para diferentes valores del parametro de control L : A, steady state ($L = 4$, ss_s) ; Limit cycle (B, $L = 3$; C, $L = 2$; D, $L = 1$); r (red), x (blue) and y (green) (For interpretation of the references to color in this figure legend, the reader is referred to the webversion of this article).

In this way, we see that according to our conjecture, there is a fine regulation of the ferroptosis process of carcinogenic cells. In fact, as seen in Fig. 3, as the control parameter values decreases, there is a predominance of tumor cells compared to the other species and an increase in their population.

4. Thermodynamics framework

According to the seminal work of Posch–Hoover [Posch & Hoover, 1998] and Gaspard [Gaspard, 2004] the

production of entropy per unit of time $\frac{dS_i}{dt}$ can be evaluate

through of the spectrum of Lyapunov exponents λ_j by means of the relationship

$$\frac{1}{k_B} \frac{dS_i}{dt} = - \sum_j \lambda_j > 0 \quad (4.1)$$

Where the spectrum of Lyapunov exponents.

In previous works we have shown how the entropy rate [Izquierdo-Kulich, *et al.*, 2011] constitutes an index of

robustness of tumors. As shown in Table 2, as the complexity (measured through the Lyapunov spectrum) of avascular and vascular tumor growth decreases, the

ferroptosis process is favored, as we commented previously, which leads to an increase in its.

Table 2. Complexity vs. robustness for the ferroptosis of cancer cells.

Dynamic state	L	Complexity Lyapunov exponents λ_j	Robustness $\frac{dS_i}{dt}$
ss, stable focus	4	$\lambda_1 = -0.157$, $\lambda_2 = -0.159$, $\lambda_3 = -8.048$	8.37
Limit cycle	3	$\lambda_1 = 0.00$, $\lambda_2 = -0.15$, $\lambda_3 = -6.626$	6.48
P2 (2-period)	0.57	$\lambda_1 = 0.00$, $\lambda_2 = 0.00$, $\lambda_3 = -1.957$	1.98
P4 (4-period)	0.42	$\lambda_1 = 0.00$, $\lambda_2 = 0.00$, $\lambda_3 = -1.718$	1.76
Shilnikov's chaos	0.3	$\lambda_1 = 0.044$, $\lambda_2 = 0.00$, $\lambda_3 = -1.587$	1.55

5. CONCLUSIONS AND REMARKS

Our model accurately captures the basic characteristics of the ferroptotic response, an important first step towards elucidate the main requirements of the ferroptosis process. In this sense, the proposed network model generalizes, at least qualitatively, the main features of the ferroptosis processes associates with avascular and vascular tumor growth. If the proposed conjecture (the PUFAs oxidized species are those that induce the ferroptosis process) is correct, the obtained bifurcation diagram can be used to establish different therapeutic strategies against cancer based on the stimulation of ferroptosis.

Summarizing, in this paper we have found that.

1. The ferroptosis appear as a type of “first order phase transitions”, even for a range of discrete values of the control parameter L . Appraisal of ferroptosis as a process featured by criticality and threshold values may help in finding treatment strategies aimed to modify the overall process by targeting the singularities.
2. The avascular and vascular tumor growth exhibit Shilnikov's chaos dynamical behavior. The transition is tightly influenced by the control parameter L , representing by the represents the population of the oxidized PUFAs fragments.

We hope that the theoretical framework herewith described may help in establishing critical experiments that would improve our understanding of the ferroptosis processes in cancer evolution as well as finding optimal pathways for future treatments.

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