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Review

Longevity, Aging and Cancer: Thermodynamics and Complexity

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Abstract: From the formalism of the thermodynamics of irreversible processes and the theory of complex systems, characterization of longevity and aging and its relationship with the emergence and evolution of cancer was carried out. It was found that: 1. The rate of entropy production can be used as an index of robustness, plasticity, the aggressiveness of cancer, and as a measure of biological age; 2. The aging process, as well as the evolution of cancer, goes through what we have called "biological phase transition"; 3. The process of metastasis, which occurs through epithelial-mesenchymal transition (EMT), appears as a phase transition far from thermodynamic equilibrium and exhibits Shilnikov chaos-like dynamic behavior. This dynamic guarantees the robustness of the process and, in turn, its unpredictability; 4. It was shown that as the ferroptosis process is strengthened, the complexity of the dynamics associated with the emergence and evolution of cancer decreases. The theoretical framework developed contributes to a better understanding of the biophysical-chemical phenomena of longevity and aging and their relationship with cancer.

Keywords: longevity; aging; cancer; complex systems; non-equilibrium thermodynamics; biological phase transition; ferroptosis

1. Introduction

Longevity and aging remain one of the most intriguing and captivating topics in human knowledge. Despite the achievements of biomedical sciences, the mechanism of aging processes remains unknown and generates great controversy [1]. Aging is manifested through the so-called degenerative diseases, such as cardiovascular disorders, cancer, atherosclerosis, diabetes, and senile Alzheimer's dementia (SDAT), among others [2-4]. The incidence of all these degenerative diseases increases exponentially with age.

Medvedev in 1990 [5] compiled around 300 theories on aging and the number has grown to this day [6]. There is currently a consensus that the aging process is multifactorial and complex, which is the main difficulty in arriving at a unified theory.

In general, aging theories can be grouped into three large groups: 1. Those related to the action of reactive oxygen species, ROS; 2. Theories that establish a link between metabolic rate and longevity; 3. Finally, those that try to explain aging from a thermodynamic point of view.

According to Harman's theory [3,7], the main factor inducing aging processes is the deleterious action of free radicals, ROS, on biopolymers. Free radicals are capable of reacting with nucleic acids, DNA, proteins, and polysaccharides causing structural damage which leads to their loss of functionality, as well as the appearance of unwanted species. This leads to progressive loss of physiological integrity, leading to impaired function and increased vulnerability [8].

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According to Sohal's theory [9], the rate of aging and the metabolic rate of organisms are inversely correlated. The effects of metabolic rate on aging may be mediated by ROS. Antioxidant defenses tend to decline during aging, while ROS-induced damage increases with age.

The third group of theories on aging [10-14], no less important than the previous ones, has guided the approach to the aging process from a thermodynamic point of view. This systems analysis approach can offer an integrated picture of a phenomenon as complex and multifaceted as aging.

All of these approaches are closely related and consider various facts, including how aging works through degenerative or complex diseases. Within the group of so-called degenerative diseases, cancer is the second cause of death worldwide according to the WHO [15], and it is estimated that the number of new cases will increase in the coming years.

As we have previously defined [16], cancer can be considered as a complex network of cells that have lost their specialization and growth control and that appear through what we can call "biological phase transition", which leads to spatial and temporal self-organization out of thermodynamic equilibrium since it exhibits high robustness and adaptability [17].

The lethal stage of cancer manifests itself through metastasis. The appearance of the metastatic process appears abruptly, recalling a type of "first-order" phase transition [18]. The chances of survival are lower compared to the previous stages, thus exhibiting greater robustness and a higher level of the hierarchy, which competes with the different levels of the hierarchical and the functional organization of the organism. This is, therefore, why a tumor is considered cancer, given its ability to metastasize.

There is sufficient evidence [19-21] concerning the complexity of cancer and despite the achievements of molecular biology and genomics, the mechanism of tumor cell growth and the nature of its robustness are still unknown.

The thermodynamic formalism of the aging process for biological systems allows us to see this problem as a whole, taking into account that the "whole" is more than the sum of its parts. Concerning longevity and aging and its relationship with degenerative diseases, particularly cancer, two basic questions arise: 1. When does the aging process begin? 2. How does the appearance of degenerative diseases, particularly cancer, manifest as part of the aging process?

Our objective is to offer a general landscape of longevity and aging and its relationship with the appearance and evolution of cancer from the point of view of the thermodynamics of irreversible processes for nonlinear systems, that is, the formalism of the thermodynamics of complex processes [22,23]. The work is structured as follows: Section 2, offers a brief introduction to the formalism of the thermodynamics of complex processes, such as, nonlinear systems. Section 3 is dedicated to longevity and aging and their relation to the emergence and evolution of cancer. The process of ferroptosis and cancer is addressed in section 4. Finally, some concluding remarks are presented.

2. Overview of the formalism of the thermodynamics of complex processes

This Section presents an overview of the thermodynamic formalism of irreversible processes on nonlinear dynamical systems and their relationship with complex systems [22,23]. On the one hand, it is shown how the rate of entropy production constitutes *per se* a natural Lyapunov function for those nonlinear systems [24], which allows us to generalize an extremal criterion on a macroscopic scale for natural systems.

On the other hand, an extension is made to biophysical-chemical systems that shows how the rate of entropy production represents a physical quantity to measure the robustness, plasticity, and aggressiveness of cancer [25].

Already in the formulation of the second law within the formalism of classical thermodynamics, it is possible to establish an evolution criterion for the macroscopic pro-

cesses of natural systems, that is, the entropy production is positive and zero at equilibrium $d_i S \geq 0$, which represents the general criterion of irreversibility [26]. However, in the classical formulation of the Second Law, the main limitation is that it does not contain time within its formal structure, which imposes a fundamental restriction on the classical formalism of thermodynamics.

In order to overcome this limitation, the formalism of the so-called thermodynamics of irreversible processes was developed. In the seminal works of Onsager [27], de Groot-Mazur [28] and Prigogine [29], the foundations of the thermodynamics of irreversible processes were established. Formally, it is divided into two: the linear region and the non-linear region. Although the formalism of the linear region is solidly established, both in its theoretical foundation and its experimental verification, the nonlinear region is still in its infancy [30].

The formal structure of the thermodynamics of linear irreversible processes is based on the existence of linear relationships between forces and generalized flows [26]. When there is no such phenomenological relationship, then we speak of the non-linear region.

It is important to highlight the fact that the linearity of dynamic systems should not be confused with the existence of a linear dependence between flows and generalized forces. For example, a phenomenon such as heat conduction, typically nonlinear, the phenomenological equation that governs it is the well-known Fourier equation [26], that is, the formalism of linear irreversible processes already deals with phenomena of order natural non-linear nature, consequently, can give rise to complex processes.

The seminal work of Prigogine *et al.* [32], on the so-called "dissipative structures", established an appropriate theoretical and practical framework for the thermodynamic approach to biological systems. In fact, it constitutes the foundational basis of the so-called Systems Biology [33].

The complexity exhibited by dissipative structures, as a dynamical system, is due to the spatial and/or temporal self-organization [33] that occurs far from thermodynamic equilibrium resulting from a bifurcation [34]. The bifurcations in dynamical systems are the analog of [35] phase transitions in the vicinity of equilibrium and are the consequence of microscopic fluctuations that grow and amplify to the macroscopic level, thus representing the fundamental mechanism of origin of self-organization far from equilibrium [31] and, therefore, of complexity at the macroscopic level [36]. In this way, thermodynamics constitutes the theoretical foundation and, in turn, an essential tool in the study of complexity.

The generalized expression of the Second Law establishes the starting point of the thermodynamic formalism [26], thus we have

$$\frac{dS_S}{dt} = \frac{d_e S}{dt} + \frac{d_i S}{dt}. \tag{1}$$

where $\frac{dS_S}{dt} \equiv \dot{S}_S$ is the entropy change of the system per unit time, $\frac{d_e S}{dt} \equiv \dot{S}_e$ is the rate of entropy exchange with the surroundings or flow, and $\frac{d_i S}{dt} \equiv \dot{S}_i$ is the rate of entropy production due to irreversible processes occurring within the system. The Eq. (1) can be rewritten as

$$\dot{S}_S = \dot{S}_e + \dot{S}_i. \tag{2}$$

Thus, the evolution criterion $\dot{S}_i \geq 0$ can be generalized as which in fact constitutes one of the postulates on which the formalism of irreversible processes rests and the essence of the Second Law.

In order to generalize the evolution criterion and formulate an extremal principle, Prigogine demonstrated how the production of entropy per unit of time is a physical mag-

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nitude that constitutes a natural Lyapunov function [37], known as the "General Evolution Criterion" [38], as long as there is a linear dependence between the flows and the generalized forces, which is restricted to the linear region of irreversible processes.

At the end of the 19th century, Lyapunov, in parallel with Poincaré, mathematically developed a method known as the Lyapunov function, which allows knowing the evolution and global stability of the dynamics of a system [39].

Let be a p fixed point, steady state, of a flow $\frac{dx}{dt} \equiv \dot{x} = f(x)$, a function $V(x)$ is called Lyapunov function of p if for some neighborhood N of p the following conditions are met:

1. $V(x) > 0$ for everything $x \neq p$ in N and $V(p) = 0$;
2. The Eulerian derivative, $\frac{dV(x)}{dt} \leq 0$ for all x in N.

In this way it can be affirmed that for all $t \geq t_0$, p it is globally and asymptotically stable, that is, the system evolves towards a minimum of the function $V(x)$, which constitutes *per se* an extremal principle.

In previous works [24], we showed, on the one hand, for nonlinear systems, namely chemical reaction, how the rate of entropy production is a Lyapunov function depending on the control parameters, that is, those parameters that determine the quality of the dynamics of a dynamical system. This approach makes it possible to generalize the evolution criterion and thus formulate an extremum criterion, such as

$$\begin{aligned} &\dot{S}_i = f(\Omega) > 0, \\ &\frac{d\dot{S}_i}{dt} = \frac{\partial \dot{S}_i}{\partial \Omega}\frac{d\Omega}{dt} \leq 0; \end{aligned} \tag{3}$$

where Ω is the vector of control parameters (analogous to the critical parameters in phase transitions, which determine the quality of the system dynamics).

On the other hand, as an extension to biological systems, we show how the rate of entropy production can be used as an index of robustness, plasticity, and aggressiveness of cancer, and, in turn, as a measure of biological age [16,40,41].

Thus, we have that by Ansatz (a term often used in physics-mathematics, is an estimated solution to an initial equation that describes a physical or mathematical problem) we established a functional dependence of the entropy per unit of time with the fractal dimension of the tumor and its growth rate [25] as:

$$\dot{S}_i = R\dot{\xi}\ln\left(\frac{5-d_f}{1+d_f}\right). \tag{4}$$

Formula (4) includes two properties observed in tumors: their growth rate $\dot{\xi}$, a measure of aggressiveness, and another, their malignancy related to their morphological characteristics, that is, the fractal dimension d_f; the ability of the tumor to invade and infiltrate healthy tissue.

According to Prigogine [26] for living organisms the rate of entropy production of living organism can be measured by its metabolism, through the rate of evolution of energy in the form of heat $\dot{q}$ as

$$\dot{S}_i \approx \frac{\dot{q}}{T}. \tag{5}$$

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According to Zotin [42], the rate of evolution of energy in the form of heat $\dot{q}$ can be determined in biological systems measured the rate of oxygen consumption $\dot{q}_{O_2}$, oxidative phosphorylation (OxPhos), through the basal metabolic rate (BMR) and the glycolytic rate $\dot{q}_{Gl}$, as

$$\dot{S}_i = \frac{\dot{q}_{O_2} + \dot{q}_{Gl}}{T}. \quad (6)$$

For healthy humans, under aerobic conditions, the glycolytic rate term is negligible except in cancer patients where the glycolysis process is predominant [43]. In this case, the rate of entropy production can be determined from the formula, Eq. (6) as:

$$\dot{S}_i \approx \frac{\dot{q}_{O_2}}{T}. \quad (7)$$

The formula, Eq. (6) is useful to evaluate the rate of entropy production of living organism through calorimetric measurements.

3. Longevity and aging and their relationship with the emergence and evolution of cancer

From the data reported by Boothby *et al.* [44] the rate of entropy production, Eq. (6), was evaluated for healthy humans of different ages, as shown in Figure 1.

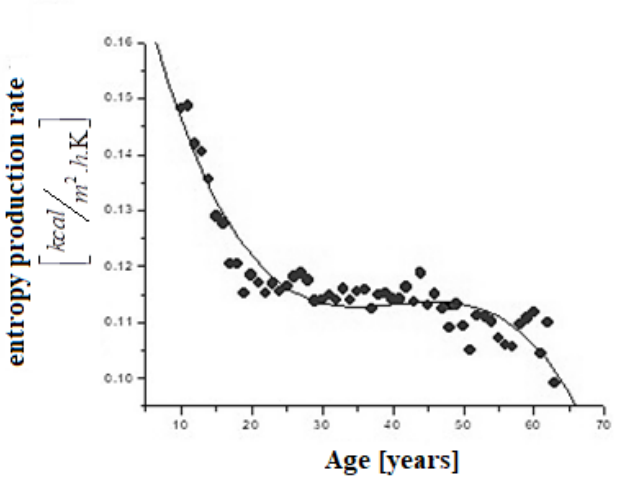

Figure 1. Dependence of the rate of entropy production per unit surface area of the individual healthy humans under basal conditions. The best fitting curve was determined to be cubic as a function of age with the parameters: $\alpha = 0.194 \pm 0.006$, $\beta = \text{-}0.0062 \pm 0.0006$, $\gamma = 1.6\text{E-}4 \pm 2\text{E-}5$, $\delta = -1.3\text{E-}6 \pm 2\text{E-}7$; R-square = 0.88505, SD=0.00349, N=54, P<0.0001.

From the data in Fig. 1, a polynomial fit of the following type is found:

$$\dot{S}_i = \alpha + \beta\ \Omega + \gamma\ \Omega^2 + \delta\ \Omega^3. \quad (8)$$

where Ω represents the age of the human. The regression, Eq. (8), resembles the van der Waals [45] equation of state, which is useful for describing first-order phase transitions. Thus, a parallel can be drawn between the van der Waals equation of state and Eq. (8). On the one hand, it is observed (see Figure 1) how the aging processes are started around the age of 20, which coincides with what is already that accepted in the literature [46], that is, there appears a phase transition resembling a "first order" phase transition.

Obviously, these calculations are approximations. On one hand, it is observed how the trend from the age of 20 clearly shows that the aging processes begin to be activated. On the other hand, the entropy production per unit time decreases, which, as we have shown in previous works, implies a decrease in complexity [25], that is, the system is less robust, therefore more sensitive to internal and external perturbations.

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The experimental facts indicate this trend, for example, the respiratory capacity of the human being is optimal and begins to decline, interestingly, from the age of twenty [47]. In addition, it has been found that the complexity of the heart rhythm changes with the age of the healthy individual, moving from more complex electrocardiograms to simpler ones [48] and finally to periodic ones. It has also been seen in patients with heart disease, where a certain periodicity appears [49].

This evidence gives us a plausible reason to believe that the aging process goes through what could be called "biological phase transitions" [40].

On the other hand, it is observed that, with increasing age, the rate of entropy production decreases (see Figure 1), that is, the complexity decreases [50], an aspect that has been pointed out by other authors [51].

Thus, the production of entropy per unit of time meets the necessary and sufficient conditions to be a Lyapunov [39,41] function. If we take the age of the subjects as a control parameter $\left(\Omega \equiv \text{age}\right)$, (Eq. (3), we have that the Eulerian derivative must satisfy:

$$\frac{d\dot{S}_i}{dt} = \frac{\partial \dot{S}_i}{\partial \Omega}\frac{d\Omega}{dt} \leq 0. \tag{9}$$

Naturally Ω, it is related to chronological age, therefore, we have $\frac{d\Omega}{dt} > 0$, then it is true that $\frac{\partial \dot{S}_i}{\partial \Omega} \leq 0$ which can be shown from Eq. (8) and as shown in Figure 1. This allows us to state that the rate of entropy production is a Lyapunov function, that is, it shows the directional character of the aging process. Furthermore, it would alternatively be a quantitative indicator of the biological age of humans [46].

We thus come to postulate that the initiation of aging processes occurs naturally for biosystems. This conjecture is in agreement with the theory given by Cutler [52] where each species of mammal is characterized by a particular lifespan. Physiological and psychological changes that occur with aging have been shown to indicate the biological age of the individual [53].

Concerning the second aspect: how do explain the appearance of degenerative diseases? According to Harman's theory [3,7] of free radicals, these species, ROS, are generated by chain reactions and are present in the appearance of degenerative diseases such as cancer, atherosclerosis, etc.

In the theory of Sohal [9], the rate of aging and the metabolic rate of organisms are inversely correlated. The effects of metabolic rate on aging may be mediated by ROS. Antioxidant defenses tend to decline during aging, while ROS-induced damage appears to increase with age [54]. Here precisely the link between the presented thermodynamic framework and the theories of Harman and Sohal [3,7,9] is established.

Particularly in cancer, the significant increase in the rate of glycolysis observed in tumors is well known [43,55]. Fenninger and Mider [56] have observed an elevation in basal metabolic rate in some cancer patients. Altered energy metabolism is proving to be as widespread in cancer cells as many of the other cancer-associated traits that have been accepted as hallmarks of cancer [43], few oncologists or cancer researchers understand the full scope of Warburg's work [57] despite its great importance. Hence, the regulation of metabolism would be relevant to the senescence process [58], which in turn is key to improving and identifying new cancer therapies in the future.

Consequently, for humans with cancer, it is necessary to use Eq. (6) to evaluate the entropy production rate. For this we use the data reported by Holroyde *et al.* [59] for patients with metastatic carcinoma. The results showed how the rate of entropy production for cancer patients compared to healthy individuals is higher for the same age range [40]. On the one hand, this may be due to the contribution of the glycolysis process in cancer patients. On the other hand, can be interpreted as a grade of the robustness of cancer [25,60,61].

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As we have mentioned, a common property of cancer is its alteration of glucose metabolism, known as the Warburg effect [62]. It has been suggested that the presence of aerobic glycolysis in highly invasive cancerous tumors is related to their aggressiveness, indicating that the glycolytic phenotype confers a proliferative advantage during the somatic evolution of cancer, in addition to being a crucial component in its malignancy [43].

Despite the limited information available on this aspect, we established as a hypothesis [63] that cancer glycolysis is a self-organized process far from thermodynamic equilibrium, for which sustained oscillations give it high robustness and complexity [23,31,50].

For this, we developed an empirical model of ordinary differential equations, based on HeLa cervical cancer cells [63], which showed that for low glucose concentrations ([Glu]0 = 2.5 mM), as observed in Fig.2 A, the system exhibits periodic oscillations, limit cycle type.

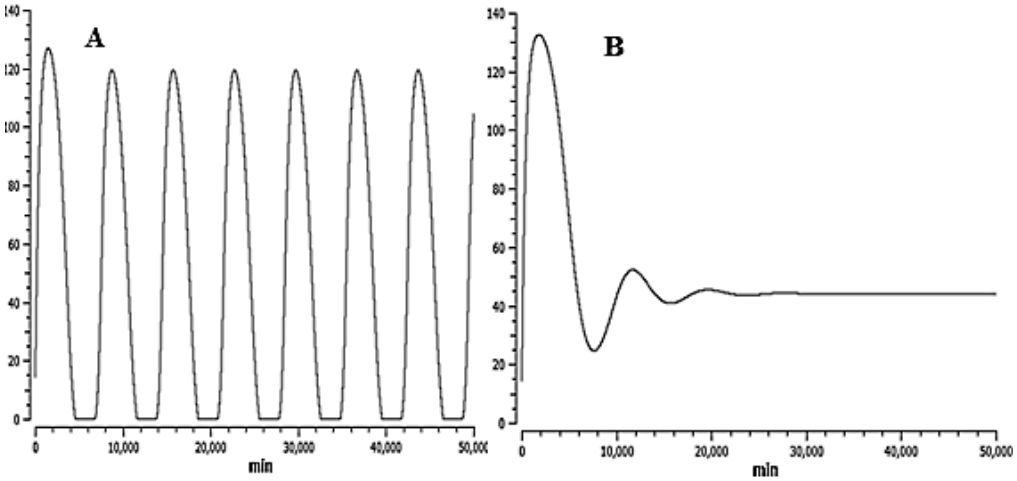

Figure 2. Time series of ATP concentration vs. time, for HeLa cervical cancer cells. **A)** $[Glu]_0$ = 2.5 mM, **B)** $[Glu]_0$ = 25.0 mM.

In a later work Takashi, *et al.* [64] experimentally showed this fact. In other words, the oscillations give the glycolytic process in cancer greater complexity, which ensures its robustness against different therapies.

In general, cancer can be seen as a "failure" of development, involving a network of interacting cells and their microenvironment, losing control over proliferation and cell fate specification [65]. This network of malignant cells, as we commented at the beginning, can be considered as a nonlinear dynamic system, self-organized in time and space, far from thermodynamic equilibrium, which presents a high complexity, robustness, and adaptability [17].

Such a process is carried out mainly through the deregulation of critical events that occur during biological transitions. Since phenotypic differentiation and cancer transformation are self-organizing processes, governed by thermodynamics far from equilibrium, fluctuations in control parameters at the bifurcation point are important. Even subtle changes in some critical values can impair the self-organization process, leading to unexpected different states, exhibiting variable robustness and adaptability within the attractive landscape [66].

It is generally accepted that cancer evolves along three basic steps [67]: avascular, vascular, and metastatic, all emerging after biological phase transitions [16]. The metastatic process consists of sequential, interconnected, and selective steps [42], and many of these are due to an obligatory transition from an epithelial to a mesenchymal phenotype [68].

An epithelial-mesenchymal transition (EMT) is a biological process that allows a polarized epithelial cell, which normally interacts with the basal surface of the membrane,

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to undergo multiple biochemical changes that allow it to assume a mesenchymal cell phenotype, including an improved migratory capacity, invasiveness, and increased resistance to apoptosis [69].

The current paradigm suggests that EMT drives metastasis by producing mesenchymal cells that escape the primary tumor and migrate to distant sites, thereby reverting to an epithelial state through mesenchymal-epithelial transition (MET). Furthermore, depending on the relationships between cells and their new microenvironment, metastatic foci may eventually spread to other organs and tissues, or enter a state of latency [70]. The EMT process has been observed in multiple epithelial tumors, such as prostate, breast, and colorectal cancer [71] among others.

Although the role of EMT is well documented in the literature [72], there are few reports dealing with the dynamics of EMT [72,73]. Indeed, most dynamical, and statistical models of EMT focus on the genetic and biophysical changes associated with EMT [74].

In this sense, we develop an empirical model, based on ordinary differential equations, ODE [75], which qualitatively models and rescues the main details of the metastasis process and involves the epithelial-mesenchymal transition process (EMT), which is shown schematically in Figure 3.

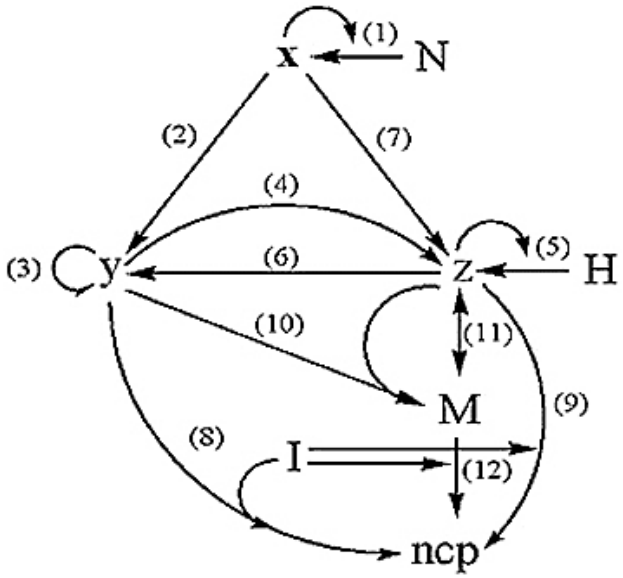

Figure 3. Graph of the process of epithelial-mesenchymal transition, EMT during metastasis.

In the model, Fig.3, ***N*** represents the population of normal cells exposed to the procancer stimulus; ***H*** is the population of host cells in the environment surrounding the tumor [76], which exclusively includes epithelial cells; ***I*** is the population of immune cells (T lymphocytes (CTL) and natural killer (NK) cells) [77], ***M*** is the population of mesenchymal cells. ***N*** and ***H*** are considered constant (because these cell groups are much more numerous than cancer cells and for practical purposes, their number does not change) and we postulate that the population of immune cells ***I*** is the control parameter (since the population of cells immune systems may fluctuate or maybe boosted through therapy). The variables: ***x***, ***y***, and ***z*** represent the population of epithelial tumor cells in the avascular, vascular and metastatic states, respectively. Finally, ***ncp*** represents a noncancerous product due to the action of immune cells.

Steps 1, 3 and 2, 4, 6 are related to the process of mitosis and apoptosis of proliferating tumor cells, respectively; steps 5 and 7 correspond to the action of the host ***H*** [76]; steps 8, 9 and 12 show the action of immune cells I. Finally, steps 10 and 11 are related to EMT. Step 10 represents an intermediate preparatory step of the epithelial cell before its transition to the mesenchymal phenotype [78].

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The model shows (see Fig. 4), that for a critical value of the control parameter ***I***, tumor cells exhibit "apparently random behavior" (remnant of Shilnikov-like chaos [79,80] when challenged by immune system activation). That hypothesis has been vindicated by a recent study, demonstrating that a mesenchymal phenotype correlates with immune evasion through reduced immunoproteasome expression, the underlying mechanism of immunoproteasome regulation involving STAT3, STAT1, and miR-200s [81].

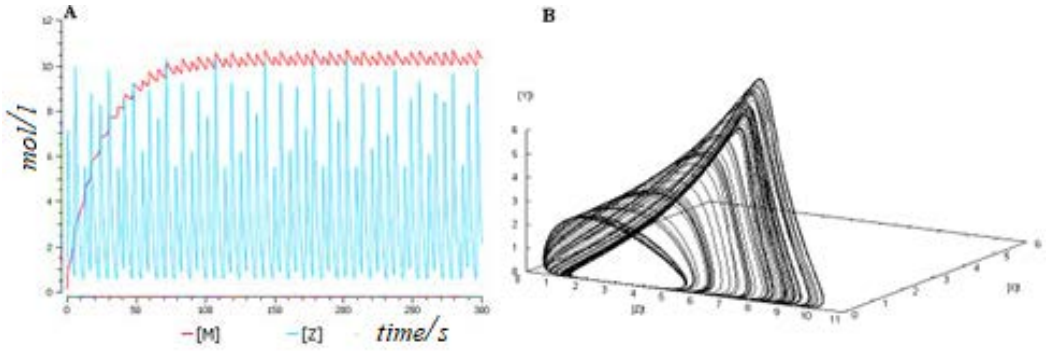

Figure 4. Time series of the dynamics of the EMT for the proposed model (Fig.3), for control parameter values ***I***=0.4, epithelial cells (light blue) and mesenchymal cells (red); **B**. Chaotic attractor.

This behavior has important biological implications. On the one hand, the high sensitivity of the system to the initial conditions makes long-term predictions about the evolution of the EMT unfeasible, that is, the final forecasts are unlikely (bad forecast).

Furthermore, the system shows a high degree of robustness [82,83]. This implies that cancer cells are resistant to drug treatment, leading to a low response rate, especially when the cancer is in a metastatic state [84].

Additionally, the information created during the evolutionary process, cannot be destroyed [85], which is clinically manifested in the recurrence (relapse) of cancer after a time that has apparently been "eliminated" [86,87]. Mechanisms of drug resistance developed during the multiple transition affecting cancer development are still maintained even after successful primary chemotherapy intervention and maintain a high rate of clinical recurrence [86,87].

We see how the EMT transition during metastasis appears as a "first order phase transitions" type, for a range of discrete values of the order parameter and a continuous spectrum of transitions from one phenotype to another can be recognized both from the model and from the experimental data. Evaluating EMT as a process characterized by criticality and threshold values can help find treatment strategies aimed at modifying the overall process by targeting singularities. This approach would likely focus on reversing the cancer phenotype rather than simply killing cancer cells, a goal that is hardly achieved with current chemotherapy regimens [88].

4. Ferroptosis and cancer

Ferroptosis is a process of iron-dependent programmed cell death, characterized by the accumulation of reactive oxygen species (ROS), such as lipid peroxides, radical superoxide, hydroxyl radical, hydrogen peroxide, etc.; and it is genetically and biochemically distinct from other forms of regulated cell death, such as apoptosis [89].

Most cancer therapies, such as chemotherapy and radiotherapy, show little effectiveness, especially in the stages of vascular growth and metastasis. It is well known that only 60% of different types of cancer can be cured with conventional therapies, and they are also accompanied by undesirable side effects [90]. On the other hand, it is known that in many types of cancer the process of apoptosis, programmed cell death, is repressed [91].

Three essential characteristics define the ferroptosis process [92], namely: 1. The loss of the ability to repair damage caused by lipid peroxides by glutathione peroxidase GPX4,

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2. The availability of iron redox-active and 3. the oxidation of phospholipids containing polyunsaturated fatty acids (PUFA).

An important issue is whether any type of lipid peroxidation is classified as ferroptosis or whether only certain lethal types of lipid peroxidation should be designated as ferroptosis [93]. Indeed, how lipid peroxidation leads to ferroptosis remains an unsolved mystery [93].

On the one hand, there is evidence that ferroptosis processes are associated with the etiopathogenesis of various degenerative diseases such as cardiovascular disorders, cancer, atherosclerosis, diabetes, and Alzheimer's dementia (SDAT), among others [2,94], which lead to progressive loss of physiological integrity, leading to functional impairment and increased vulnerability and death [2-4].

On the other hand, in recent years, numerous studies have shown the efficacy of cancer elimination by inducing ferroptosis, which is mainly achieved by raising intracellular ROS levels and inactivating the action of GPX4 [95-97].

To the best of our knowledge, only a few ferroptosis-related models have been reported [98-100]. Kagan *et al.* [98] developed a continuous model for ferroptosis with a biochemical cascade-based approach. While the model provides an excellent synthesis of the specific processes involved, it excludes the contributions of lipid peroxidation processes involved in ferroptosis.

On the other hand, Agmón *et al.* [99] performed molecular dynamics simulations of membranes with compositions relevant to ferroptotic sensitivity and showed how the biophysical properties of membranes are altered under competent ferroptotic lipid compositions.

More recently, Konstorum [100] has developed a multistate discrete modeling approach to emphasize the qualitative properties of signaling cascades relevant to ferroptosis. The discrete modeling approach allows the relative importance of different ferroptosis promoters to be explored using a wider range of data than would be available for a detailed kinetic model of the system.

To the authors' knowledge, there is no model that connects the lipid peroxidation processes involved in ferroptosis with the growth of cancer cells.

Despite there being sufficient evidence and consensus in the literature related to ferroptosis-mediated anticancer effects [101,102], on the one hand, the mechanisms underlying each step of this complex process remain unclear [93,99]. On the other hand, there is no model that connects the lipid peroxidation processes involved in ferroptosis with the growth of cancer cells.

In this sense, we proposed a heuristic model [103] that connects lipid peroxidation, the evolution of cancer cells in the avascular and vascular phases [67] and the ferroptosis process. The model contains three species of populations: $r(t)$-lipid peroxides, $x(t)$-avascular tumor cells, and $y(t)$-vascular tumor cells.

Figure 5 shows the graph structure of the proposed cancer ferroptosis model [103], where a connection is established between lipid peroxidation, the evolution of cancer in the avascular and vascular phases, respectively, and the ferroptosis processes.

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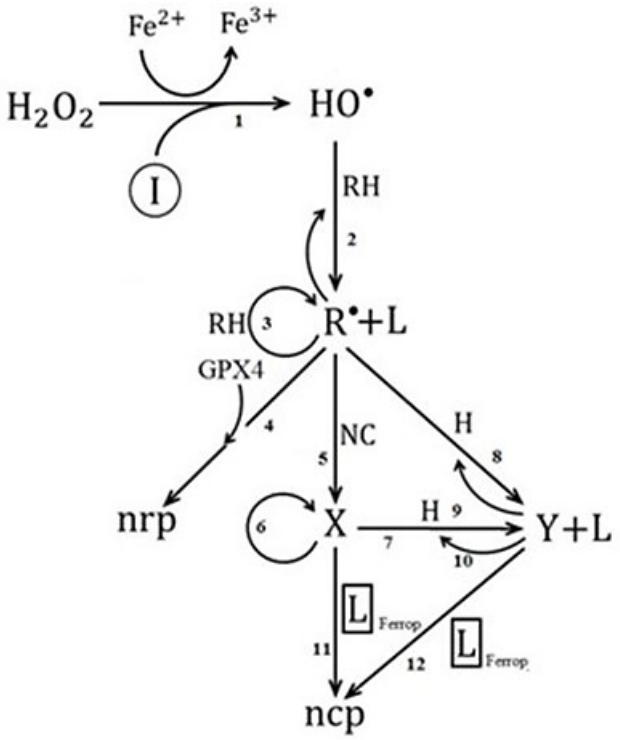

Figure 5. Graph of the model of ferroptosis of cancer in avascular and vascular growth.

In the model (Figure 5), I symbolizes ferroptosis-inducing agents, such as iron-based nanomaterials, e.g., ferumoxytol, amorphous iron nanoparticles, induced ionizing radiation, etc. [104,105]; H_2O_2 is hydrogen peroxide; HO^* are the hydroxyl radicals; RH represents polyunsaturated fatty acids (PUFAs); NC is the population of normal cells exposed to pro-cancer stimuli; H it is the population of host cells in the environment surrounding the tumor [76], composed exclusively of epithelial cells; $\mathrm{GPX4}$ is glutathione peroxidase 4; L represents the population of oxidized PUFA fragments [99].

In this sense, it was established as a conjecture that the population of oxidized PUFA fragments L are those that favor the ferroptosis process of cancer cells [103]. For this reason, we take L as control parameter (CP), that is, whose value changes the quality of the system dynamics.

The variable species represent: $r(t)$-lipid peroxides, $x(t)$-avascular tumor cells, and $y(t)$-vascular tumor cells, respectively. Finally, ***nrp*** and ***ncp*** represent non-radical products and non-cancerous products, respectively.

Step 1 is associated with the Fenton reaction [106], step 2 is related to the formation of lipid peroxides [107], step 3 is the propagation of lipid peroxidation chain reactions [108], step 4 is the main cellular mechanism of protection against reactive oxygen species (ROS), which is mediated by the action of glutathione peroxidase 4 [109]. steps 5, 6 and 7, 10 are related to the process of mitosis and apoptosis of proliferating tumor cells, respectively; steps 8 and 9 correspond to the action of the host cells [76], finally, steps 11 and 12 are related to ferroptosis and vascular avascular tumor growth, respectively.

In Figure 6**A** the dynamic behavior of the proposed model is shown. It is observed that for low values of the control parameter L, tumor cells exhibit an "apparently random behavior" (remnant of Shilnikov-like chaos) [80], with a predominance of the population of vascular tumor cells (green).

This behavior has important biological implications. On the one hand, the high sensitivity of the system to the initial conditions makes long-term predictions unfeasible (bad

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forecast). In addition, the dynamic system of cancer evolution presents a high degree of complexity [82,83]. This implies that cancer cells are resistant to drug treatment, leading to a low response rate [84].

As can be seen (see Fig. 6D) the increase in the population of the oxidized PUFA fragments L (control parameter), produces an inverse Feigenbaum scenario (a cascade of saddle-foci Shilnikov's bifurcations), which leads to the stabilization of the dynamics and a decrease in the complexity of the system.

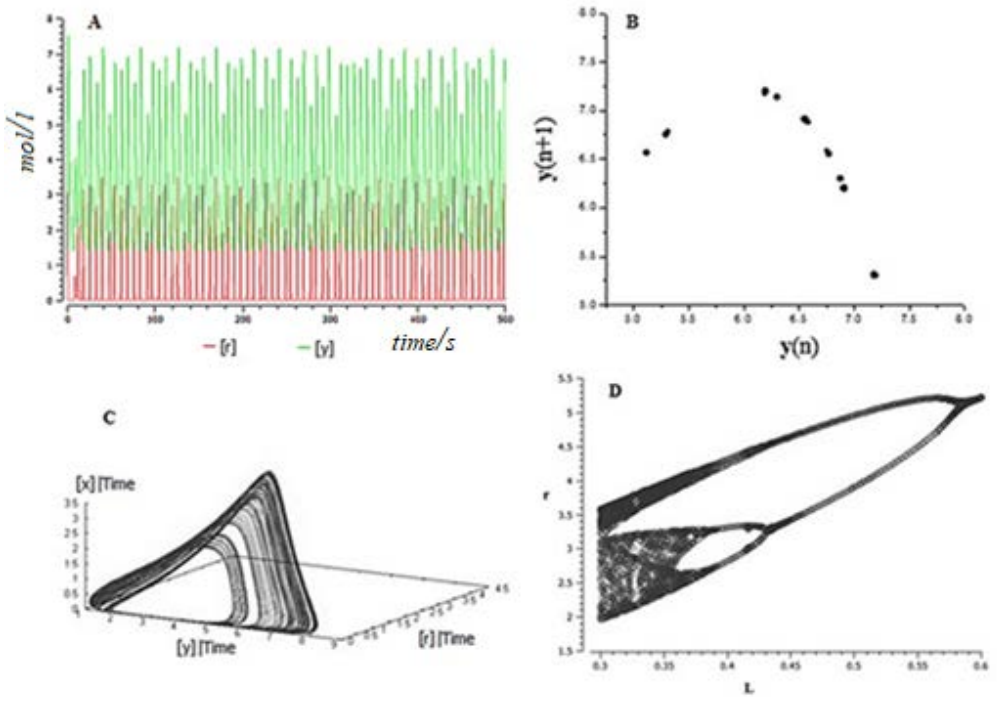

Figure 6. Dynamics of ferroptosis tumor growth for the proposed model (Fig. 5), for the value control parameter $(L = 0.3)$; **A**. time series; **B**. Iterated unimodal map obtained from tracing successive local maxima of the temporal dynamics of vascular tumor cells (green); **C**. Chaotic attractor; **D**. Bifurcation diagram obtained from r_{max} showing the halving scenario (i.e., inverse Feigenbaum) that occurs as inactivation of the population of oxidized PUFA fragments by tumor cells decreases.

In fact, at the critical point $L = 3.383$, a supercritical Andronov-Hopf bifurcation occurs [29], the dynamic analog of a first-order phase transition, leading to a steady state. In this way, we see that, according to our conjecture, there is a fine regulation of the ferroptosis process of cancer cells through the fragments of oxidized PUFAs L.

5. Concluding Remarks

In summary, it has been shown how the non-equilibrium thermodynamics formalism and complex systems theory offer an appropriate theoretical framework for the characterization of longevity, aging and the emergence and evolution of cancer [14,16,17,40,60,61,66,75,110-116]. It was found that:

1. The process of metastasis occurs through epithelial-mesenchymal transition (EMT), appears as a phase transition away from thermodynamic equilibrium, and exhibits Shilnikov chaos-like dynamic behavior. This dynamic guarantees the robustness of the process and, in turn, its unpredictability.

2. The aging process, as well as the evolution of cancer, goes through what we have called "biological phase transition".

3. The rate of entropy production can be used as an index of robustness, plasticity, and aggressiveness of cancer. It can also be used as a measure of biological age.

4. It was shown as to the extent that the ferroptosis process is strengthened, decreases the complexity in the dynamics associated with to the emergency and evolution of cancer.

The theoretical framework developed contributes to a better understanding of the biophysical-chemical phenomena of longevity and aging and their relationship with cancer.

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