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The Rate of Entropy Production as a Lyapunov Function in Biophysical-chemical Systems

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Abstract

An overview of the link between nonequilibrium thermodynamics and complexity theory is offered here, showing how the entropy production rate can be quantified through the spectrum of the Lyapunov exponents. The work shows how the entropy production per unit of time meets the necessary and sufficient conditions to be a Lyapunov function and constitutes *per se* an extremal principle. The entropy production fractal dimension conjecture is also established. The work demonstrates how the rate of entropy production as a non-extremal criterion represents an alternative way for sensitivity analysis of differential equations. Finally, in an extension to biophysical-chemical systems, on the one hand, the study presents the use of the dissipation function as a thermodynamic potential out of equilibrium in the characterization of biological phase transitions. On the other hand, it evidences that the entropy production rate represents a physical quantity that can be used to evaluate the complexity and robustness of cancer.

Keywords: nonequilibrium thermodynamics, entropy production rate, Lyapunov function, complexity, biological phase transitions

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Introduction

The advent of the so-called chaos theory initially (Schuster, 2006) and the more recent developments in the sciences of complexity (Nicolis & Nicolis 2007) have drastically changed the vision of science, particularly the thermodynamics of irreversible processes.

The linear region of irreversible processes lies on a well-consolidated theory (Prigogine 1947; De Groot & Mazur 1962; Katchalsky & Curran 1965). However, the non-linear region is still waiting for a formalism to be built, on the one hand, while on the other, such a formalism also should incorporate complex phenomena. A first approximation in this direction, linking the thermodynamics of irreversible processes with nonlinear dynamics, was elaborated in the seminal work of Prigogine and colleagues (Nicolis & Prigogine 1977) under the name "dissipative structures." Beck & Schlögl published the work "Thermodynamics of chaotic systems" in the 1990s (Beck & Schlögl 1993), approach the subject. Although still far from a finished formalism, these works undertook the first steps in such a direction.

An extensive list of works in the literature addresses the relationship between nonequilibrium thermodynamics and complex phenomena (Gaspard *et al.* 2007; Nicolis & De Decker 2017; Nicolis & Nicolis 2010). A thermodynamic formalism of complex phenomena should be able to answer three fundamental aspects: 1. Formulate extremal principle for complex phenomena on a macroscopic scale; 2. Establish methods to determine stability in nonequilibrium states; 3. Formalize criteria to characterize the complexity at the macroscopic level of natural systems.

This work aims to offer a unifying overview of the relationship between nonequilibrium thermodynamics and non-linear dynamics, which, even far from establishing a finished formalism, serves as a starting point for what could constitute the theoretical bases of the "thermodynamics of complex phenomena." The work is structured as follows: Section 1 summarizes the fundamental aspects of the formalism of the thermodynamics of irreversible processes in the linear region; Section 2 offers an overview of the advances between nonequilibrium thermodynamics and complex phenomena; Section 3 provides an extension to biophysical-chemical systems.

1. The Formalism of the Thermodynamics of Irreversible Processes in the Linear Region

The seminal works of Onsager (Onsager 1931), De Groot-Mazur (De Groot & Mazur 1962), and Prigogine (Prigogine 1947) established the bases of the thermodynamics of irreversible processes. This formalism was based on four fundamental pillars:

1. Accept as a fundamental postulate that the production of entropy per unit of time $\frac{\delta S_i}{dt}$, is positive definite, that is:

$$\frac{\delta S_i}{dt} \equiv \dot{S}_i \geq 0 \text{, (1)}$$

2. Validity of the Onsager reciprocity relations.

3. Fulfillment of the "local equilibrium" hypothesis.

4. The existence of linear relationships between flows and forces.

In this way, the fundamental expression of the Second Law can be generalized as

$$\frac{dS_S}{dt} = \frac{\delta S_e}{dt} + \frac{\delta S_i}{dt} \text{, (2)}$$

where $\frac{dS_S}{dt} \equiv \dot{S}_S$ is the entropy rate of the system, $\frac{\delta S_e}{dt} \equiv \dot{S}_e$ is the rate of entropy exchange with the surroundings or entropy flow, and $\frac{\delta S_i}{dt} \equiv \dot{S}_i$ is the rate of entropy production. The Eq. (2) can be rewritten as

$$\dot{S}_S = \dot{S}_e + \dot{S}_i \text{, (3)}$$

Thus, the evolution criterion can be generalized as: $\dot{S}_i > 0$, which constitutes one of the postulates on which the formalism of irreversible processes rests and the essence of the Second Law. Additionally, it gives a physical meaning to time, which has been coined in the literature as The Arrow of Time (Coveney & Highfields 1991).

Sometimes, it is convenient, as we will see later, to use, instead of the rate of entropy production, the so-called dissipation function introduced by Lord Rayleigh, $\Psi \equiv T\dot{S}_i$, since it converts the entropy production rate into an out-of-equilibrium thermodynamic potential.

Formally, the rate of production of entropy, $\dot{S}_i$, can be evaluated as

$$\dot{S}_i = \sum_k J_k X_k \text{, (4)}$$

where, J_k represents generalized flows, e.g., heat flow, substance flow, etc., and X_k are the generalized forces, that is, the causes that give rise to the appearance of flows, temperature gradients, substances, etc.

A linear relationship can be established between the flows and the generalized forces, known as the phenomenological (De Groot & Mazur 1962), which was established empirically long before the formal structure of the thermodynamics of irreversible processes was established. Hence, we have

$$J_k = L_{kk} X_k \text{, (5)}$$

where, L_{kk} is known as a direct phenomenological coefficient, for example, the coefficient of thermal conductivity, λ, diffusion coefficient, D, etc. The formal structure of the thermodynamics of irreversible linear processes is based on the existence of equality, Eq. (5), that is the validity of linear relationships between generalized forces and flows. When there is no such phenomenological relationship, we speak of the non-linear region. It is essential to highlight that linearity in dynamic systems should be distinct from the existence of the linear dependence between flows and generalized forces, Eq. (5).

Of great importance are the coupling or interference processes (Prigogine 1961), which are subject to the Curie Principle of symmetry (Prigogine 1961); for example, given any two processes that are coupled under the Curie Principle, such that

$$\begin{aligned} J_1 &= L_{11}X_1 + L_{12}X_2, \\ J_2 &= L_{21}X_1 + L_{22}X_2 \end{aligned} \text{, (6)}$$

where L_{11}, L_{22} are the straight phenomenological coefficients and L_{12}, L_{21} are known as cross-phenomenological coefficients. As we mentioned previously, point 2, concerning the so-called Onsager Reciprocity Principle, it is true that,

$$L_{12} = L_{21} \text{, (7)}$$

In other words, the so-called Onsager Reciprocity Principle (De Groot & Mazur 1962; Onsager 1931) establishes that whenever an appropriate choice is made for the flows J_k and the forces X_k, the matrix of phenomenological coefficients is symmetric. Thus, considering Eqs. (6, 7) and substituting them in Eq. (4), we have that the rate of production of entropy for the coupling is given by

$$\begin{aligned} \dot{S}_i &= L_{11}X_1^2 + \left(L_{12} + L_{21}\right) X_1 X_2 + L_{22}X_2^2 \\ &= L_{11}X_1^2 + 2L_{12}X_1X_2 + L_{22}X_2^2 \geq 0. \end{aligned} \text{, (8)}$$

The Eq. (8) is a semi-positive definite quadratic form by the Second Law. Linear algebra imposes restrictions on the phenomenological coefficients in formula (8); it must be true that

$$\begin{aligned} & L_{11} > 0, L_{22} > 0 \\ & \left(L_{12} + L_{21}\right)^2 < 4L_{11}L_{22}. \end{aligned} \text{, (9)}$$

The straight coefficients are always positive magnitudes, while the crossed ones can take any value as long as the inequality of the last expression of Eq. (9).

The stationary states, also known as fixed points in the theory of dynamical systems (Andronov *et al.* 1966), are states through which different processes, physical, chemical, biological, etc. (De Groot & Mazur 1962; Katchalsky & Curran 1965) and are of particular interest in the framework of the theory of complexity sciences (Nicolis & Nicolis 2007).

Formally, a dynamical system can be defined as the ordered pair $(\mathrm{E}, \mathrm{T}_t)$ where E represents an appropriate manifold and T_t is a one-parameter group of diffeomorphisms under the parameter t often represented by time. If one has an atlas of local charts for the manifold E, on those charts, it is possible a representation the dynamical system in the following form: $\dot{X}(t) = F(X(t))$, where F is the vector field associated with the one-parameter group of diffeomorphisms.

It is said that the solution $X(t) = X_0$ is an equilibrium position or a stationary state of the system if $F(X_0) = 0$. We further say that X_0 is an attractor of the system, if for any other solution $X(t)$, whose initial conditions are close enough to X_0, we have $X(t) \to X_0$ when $t \to \infty$.

From a nonequilibrium thermodynamics point of view (De Groot & Mazur 1962), a stationary state is formally defined as a dynamic state, for which it is true that during a finite time, the state variables and the control parameters remain constant, and dissipative flows are verified, that is to say $\dot{S}_i > 0$, in such a way that

$$\dot{S}_i = -\dot{S}_e, \quad (10)$$

That is, at the same rate that entropy is produced $\dot{S}_i$, exchanges with surroundings $\dot{S}_e$, in such a way that $\dot{S}_S = 0$. Furthermore, steady states are characterized by the number of forces k that remain constant; hence, the stationary states of an order made references to k (De Groot & Mazur 1962). For instance, in Eq. (8), assuming there is a steady state, for X_2 constant, that is, of order one, $k = 1$, we should have to verify Prigogine's Theorem of Minimum Entropy Production or Prigogine's Principle (Prigogine 1961), which ensures the stability of the stationary state, that is, out of equilibrium, which constitutes an extension of the stability criterion in the vicinity of the equilibrium, Gibbs-Duhem Principle (Kondepudi & Prigogine 1998). In this way, Prigogine's Principle represents, in fact, an extremal principle if the linear relationships between flows and forces are fulfilled—Eq. (5).

Glansdorff and Prigogine tried to generalize Prigogine's Principle, known as the "general criterion of evolution" (Glansdorff & Prigogine 1971), demonstrating how the rate of entropy production, Eq. (8), constitutes from physics, a natural Lyapunov function (Mawhin 1996). According to the procedure proposed by Glansdorff and Prigogine, the entropy production per unit of time $\dot{S}_i$ is identified as a Lyapunov function, $V(x)$, $\dot{S}_i \equiv V(x)$, such that

$$\begin{aligned} &\dot{S}_i \equiv V(x) \geq 0, \\ &\frac{d\dot{S}_i}{dt} \leq 0. \end{aligned} \quad , (11)$$

The Eulerian derivative of the entropy production rate, Eq. (4), is given by

$$\begin{aligned} \frac{d\dot{S}_i}{dt} &= \sum_k J_k \frac{dX_k}{dt} + \sum_k X_k \frac{dJ_k}{dt} \\ &= \frac{d_X(\dot{S}_i)}{dt} + \frac{d_J(\dot{S}_i)}{dt}; \end{aligned} \quad , (12)$$

Considering Eq. (8) and substituting in Eq. (12), one has:

$$\begin{aligned} \frac{d_X(\dot{S}_i)}{dt} &= J_1 \frac{dX_1}{dt} + J_2 \frac{dX_2}{dt}, \\ \frac{d_J(\dot{S}_i)}{dt} &= X_1 \frac{dJ_1}{dt} + X_2 \frac{dJ_2}{dt}; \end{aligned} \quad , (13)$$

Taking into account Eqs. (6), (7), and (13), and substituting in Eq. (12) is obtained

$$\begin{aligned} \frac{d(\dot{S}_i)}{dt} &= 2J_1 \frac{dX_1}{dt} + 2J_2 \frac{dX_2}{dt}, \\ &= 2\frac{d_X(\dot{S}_i)}{dt}, \quad (14) \\ \frac{1}{2}\frac{d(\dot{S}_i)}{dt} &< 0; \end{aligned}$$

In this way, it is demonstrated that formula (14), as the production of entropy per unit of time, is a physical magnitude that constitutes *per se* a Lyapunov function if there is a linear dependence between the flows and the generalized forces. As can be seen, the general criterion of evolution, formula (14), is restricted to the linear region of irreversible processes.

2. Thermodynamic Formalism of Complex Processes

As we commented at the beginning, unlike the formalism of the thermodynamics of irreversible processes in the linear region, where most of its precepts are consolidated, the nonlinear region is still in the making; due to this, it is still premature to speak of a finished formalism. That is why we intend to provide a landscape approach to the subject and, above all, try to articulate the thermodynamic formalism of irreversible processes with that of nonlinear dynamics so that it allows us to offer a thermodynamic approach to complex phenomena (Mansilla & Nieto-Villar 2017).

On the one hand, it is essential to be clear about what we refer to as complex (Bizzarri *et al.* 2020).

Hence, the complexity manifested by dynamical systems highlights the following general and critical aspects of understanding this phenomenon:

1. Complex should not be seen as synonymous with complicated since a system described by few degrees of freedom can exhibit high complexity during its evolution; on the contrary, a system that requires many degrees of freedom to be able to describe itself and which is therefore complicated, may or may not exhibit complex behavior.

2. Complexity manifests itself through the appearance of emergent properties. These are macroscopic observables that can only sometimes be deduced from the interaction rules that govern the evolution of the different components of the systems.

3. The dimension of the patterns, both temporal and spatial, is generally not an integer and is greater than its topological dimension; therefore, they are said to have a fractal dimension (Betancourt-Mar *et al.* 2016).

4. On many occasions, the complex processes described through deterministic dynamic systems show a sensitive dependence on the initial conditions. This behavior can be confused with stochastic processes and is known as deterministic chaos (Strogatz 2000). The most important consequence of this property is the impossibility of making predictions about the system's evolution in the long term. In other words, the so-called Laplacian determinism collapses.

5. For a deterministic dynamic system to exhibit complex behavior, it must meet two fundamental requirements: nonlinear and that feedback processes exist (Nieto-Villar *et al.* 2013).

6. The fundamental mechanism that describes a system's emergent properties and complexity is based on the occurrence of bifurcations (Nicolis 1972; Nicolis & Daems 1998), a dynamic analog of phase transitions. The bifurcations exhibit a universal character in their phenomenology (Kuznetsov 2013), making them independent of the system's characteristics and representing a source of innovation and diversification because they give systems a new type of solution. The fluctuations, which have a microscopic origin, grow and amplify until they reach the macroscopic level, which leads to a break in the spacetime symmetry, giving rise to self-organization outside of thermodynamic equilibrium, the establishment of order, and coherence on a macroscopic scale, and consequently to the appearance of complexity.

Hence, the term complex should not be seen as a synonym for complicated; that is, dynamic systems self-organize temporally and spatially out of thermodynamic equilibrium, a term coined by Prigogine as Dissipative Structures (Prigogine 1978), which gives rise to the manifestation of complex phenomena.

On the other hand, Seth Lloyd compiled an extensive, still incomplete list of ways to measure complexity (Lloyd 2001). This include Shannon, Gibbs-Boltzmann, Renyi, Tsallis, Kolmogorov-Sinai entropies, and fractal dimension.

Even today, there is a great controversy concerning the thermodynamic formalism of irreversible processes, including Prigogine's Principle of Entropy Production. According to Bruers (Bruers 2006), at least "six principles" can be mentioned: 1. Principle of minimum dissipation close to equilibrium; 2. Principle of minimum production of entropy near equilibrium; 3. Principle of maximum production of entropy near equilibrium; 4. Non-variational principle far from the equilibrium of maximum production of entropy; 5. Variational principle far from the equilibrium of maximum production of entropy; 6. Optimization of the principle of minimum production of entropy.

Chemical reactions constitute an ideal model to delve into the subject since, firstly, they can occur "close to or far" from thermodynamic equilibrium, and, secondly, there is no linear relationship between the generalized flow, the rate of reaction $\dot{\xi}$, and generalized force, an affinity for the inverse of temperature $\frac{1}{T}\mathcal{A}$. Furthermore, their dynamics exhibit a wide range of temporal and spatial complexity (Nieto-Villar & Velarde 2001), and the developed formalism can be extended to biological systems.

Briefly, we will show how it is possible to generalize, at least for chemical and biological processes, the "general criterion of evolution" of Glansdorff-Prigogine (Glansdorff & Prigogine 1971), demonstrating how the rate of entropy production is a Lyapunov function without the need for the linear relationships between flows and forces hold.

Lyapunov, in his 1892 doctoral thesis (Mawhin 1996), developed a mathematical method that allowed knowing the evolution and global stability of a dynamical system, known as the Lyapunov function $V(x)$ (see Fig. 1 in Appendix). Thus, we have succinctly that:

Let p be a fixed point, a steady state of a flow $\frac{dx}{dt} \equiv \dot{x} = f(x)$, such that, if for some neighborhood N of p the following conditions hold:

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

The function $V(x)$ is called Lyapunov´s function. Thus, it can be stated that for all $t \geq t_0$, p is stable, and if $\frac{dV(x)}{dt} < 0$, the equilibrium position is asymptotically stable.

On the one hand, we show that the entropy production per unit time, at least for chemical reactions, meets the necessary and sufficient conditions of a Lyapunov function (Nieto-Villar *et al.* 2003) and, in fact, constitutes an extremal criterion *per se*, regardless of whether the network of chemical reactions is "near" or "far" from equilibrium. Recently, it has been demonstrated in reaction-diffusion-type systems (Ledesma-Durán & Santamaría-Holek 2022).

On the other hand, it was shown (Nieto-Villar *et al.* 1995; Garcia-Fernández *et al.* 1996; Nieto-Villar *et al.* 2013; Nieto-Villar *et al.* 2022) using an Ansatz through a functional of the rate of entropy production of the control parameters of the dynamic system, Ω, as

$$\dot{S}_i = f(\Omega) > 0\,, \quad (15)$$

Thus, it is found that the Eulerian derivative of Eq. (15) holds the following:

$$\frac{d\dot{S}_i}{dt} \equiv \Im = \frac{\partial \dot{S}_i}{\partial \Omega}\frac{d\Omega}{dt} \leq 0\,, \quad (16)$$

In this way, we have the acceleration of the production of entropy rate, $\Im \equiv \frac{d\dot{S}_i}{dt}$, which constitutes *per se* a potential function out of equilibrium.

The works of Hoover and Nose (Hoover & Posch 1994; Hoover 2007) and Gaspard (Gaspard 2007) showed that the rate of entropy production $\dot{S}_i$ is related to the spectrum of the Lyapunov exponents λ_j through the relationship,

$$\frac{dS_i}{dt} \equiv \dot{S}_i \approx -\sum_j \lambda_j > 0\,, \quad (17)$$

The formula, Eq. (17), establishes *per se* a natural link between the formalism of the thermodynamics of irreversible processes and nonlinear dynamics regardless of whether the system evolves "close" or "far" from thermodynamic equilibrium.

It is known that sensitivity analysis of differential equations has been used successfully to determine the fundamental steps in a reaction mechanism (Varma 2005). Edelson's pioneering works (Edelson & Allara 1980; Edelson & Thomas 1981; Edelson 1983) allowed the identification of the fundamental steps in a mechanism and its reduction. Later, Turanyi used the method in the famous Belousov-Zhabotinsky BZ reaction (Turányi 1990; Gyorgyi *et al.* 1990; Turányi 1993), drastically reducing the model mechanism, GTF, from 81 to 42 steps.

As an alternative method to the sensitivity analysis, we proposed using the entropy production rate as a non-extremal criterion, called the Method of Dominant Steps (Nieto-Villar & Velarde 2001; Nieto-Villar *et al.* 2022; Rieumont-Briones *et al.* 1997). For this, we postulate that those steps that exhibit a greater value of entropy production would be the fundamental ones in a reaction mechanism for fixed values of the control parameters.

Let be a mechanism of reaction composed of n-reaction steps and m-species, represented by equality (18), as

$$\begin{array}{c} x_{1/i} = x_{2/i} \\ \vdots \\ x_{m-1/n} = x_{m/n} \end{array}\,, \quad (18)$$

Thus, we have that the rate of production of entropy of the step-n is given by

$$\dot{S}_{i/n} = R\left(\dot{\xi}_{+/n} - \dot{\xi}_{-/n}\right)\ln\frac{\dot{\xi}_{+/n}}{\dot{\xi}_{-/n}} \geq 0\,, \quad (19)$$

where $\dot{\xi}_{+/n}$, $\dot{\xi}_{-/n}$ are forward a reverse chemical rate of the step-n. Step n will be dominant compared to step n-1 if it is fulfilled that: $\dot{S}_{i/n} > \dot{S}_{i/n-1}$. In this way, the rate of entropy production, as a non-extremal criterion, generalizes the so-called "maximum entropy" criterion later proposed by Martyushev and Seleznev (Martyushev & Seleznev 2006) and constitutes a complementary method to the sensitivity analysis of differential equations.

The fractal dimension D_f represents one of the most important properties of an attractor of a dynamic system and a way to estimate the complexity of spatiotemporal patterns from the geometric point of view (Farmer 1982), as we mentioned at the beginning of this section. Grassberger (Grassberger & Procaccia 1983) proposed a generalization of the fractal dimension, the generalized fractal dimension D_q as

$$D_q = \lim_{\varepsilon \to \infty} \frac{S_q(R)}{\ln\left(\frac{1}{\varepsilon}\right)}, \; (20)$$

where $S_q(R)$ is the Renyi´s entropy (Rényi 1960). From the formula, Eq. (20), three basic dimensions are obtained as particular cases: D_0, D_1, D_2; the Hausdorff-Besicovitch fractal dimension D_0, the informational dimension (Farmer 1982), $D_1 = \lim_{q \to 1} D_q$, and the correlation dimension D_2. In the case of fractals, the three dimensions are approximately equal, while in multifractals, it is true that: $D_0 > D_1 > D_2$ (Farmer 1983).

An alternative and straightforward way to compute the fractal dimension of a dynamical system is through the spectrum of Lyapunov exponents. λ_j, known as the Lyapunov dimension D_L defined through the Kaplan-York conjecture (Frederickson 1983) as:

$$D_L = j + \frac{\sum_{i=1}^{j} \lambda_i}{\left|\lambda_{j+1}\right|}, \; (21)$$

where j is the largest integer for which it is true that: $\lambda_1 + \lambda_2 + \cdots + \lambda_j \geq 0$. By analogy to Eq. (21), we established through an ansatz the following conjecture: the fractal dimension of entropy production (Betancourt-Mar *et al.* 2016), defined as:

$$D_{\dot{S}_i} = j + \frac{\dot{S}_i}{\left(\sum_{i=j+1}^{n} \lambda_i\right)}, \; (22)$$

where the entropy production per unit time $\dot{S}_i$, is evaluated through the formula (17), n is the number of all Lyapunov exponents.

3. Extension to Biophysical-Chemical Systems

Finally, we will provide a brief landscape of the application of the thermodynamic formalism of complex processes in biological systems, particularly on the topic of the emergence and evolution of cancer. Non-equilibrium thermodynamics has been successfully used in studies of longevity, aging, the origin of life, and, in particular, cancer (Miquel *et al.* 1984; Balmer 1982; Nieto-Villar *et al.* 2003; Molnar *et al.* 2005; Luo 2009; Lucia 2014; Lucia *et al.* 2015; Marin & Sabater 2017; Triana *et al.* 2018; Betancourt-Mar *et al.* 2018; Montemayor-Aldrete *et al.* 2020; Mesa-Rodríguez *et al.* 2022; Michaelian 2022; Nieto-Villar & Mansilla 2022; Miranda & Souza 2023).

We must start with a formal definition: ...cancer is a complex network of cells that have lost their specialization and control of growth, and that appears through a "biological phase transition" leading to spatiotemporal self-organization outside the thermodynamic equilibrium. This exhibits high robustness, adaptability, complexity, and hierarchy, which enables the creation of new information and learning capacity (Montero *et al.* 2018).

The diagnosis of the proliferative and invasive capacity of a tumor is a complicated issue since these terms include many factors. Let us highlight two fundamental ones: aggressiveness, which is related to the speed of tumor growth, and malignancy, the ability of the tumor to invade and infiltrate healthy tissue, associated with its morphological characteristics (roughness) (Norton 2005).

The growth rate of the tumor, $\dot{\xi}$ is given by

$$\dot{\xi} = \dot{\xi}_m - \dot{\xi}_{ap}, \; (23)$$

where $\dot{\xi}_m, \dot{\xi}_{ap}$ are the rates of mitosis (cell division) and apoptosis (programmed cell death), respectively. By analogy to Eq. (19), we can evaluate the production of entropy per unit of time $\dot{S}_i$, during the growth of a tumor (Izquierdo-Kulich *et al.* 2011) as

$$\dot{S}_i = \left(\dot{\xi}_m - \dot{\xi}_{ap}\right) \ln \frac{\dot{\xi}_m}{\dot{\xi}_{ap}} \geq 0 \text{ , (24)}$$

On the other hand, we developed a method based on knowing the rates of mitosis $\dot{\xi}_m$ and apoptosis $\dot{\xi}_{ap}$ (Izquierdo-Kulich & Nieto-Villar 2013) to quantify morphological characteristics (roughness) of the tumor, the malignancy of a tumor, through the fractal dimension D_f, as

$$D_f = \left(\frac{5\dot{\xi}_{ap} - \dot{\xi}_m}{\dot{\xi}_m + \dot{\xi}_{ap}}\right) \text{, (25)}$$

Considering Eqs. (23) and (25), we can rewrite Eq. (24) depending on the rate of tumor growth, $\dot{\xi}$ and the fractal dimension of the tumor D_f as

$$\dot{S}_i = R\dot{\xi} \ln\left(\frac{5 - D_f}{1 + D_f}\right) \text{, (26)}$$

In this way, an appropriate expression is obtained, Eq. (26), to evaluate the production of entropy per unit of time $\dot{S}_i$, during the emergence and evolution of cancer, which relates to two fundamental properties of tumors: aggressiveness and malignancy (Izquierdo-Kulich *et al.* 2011). Thus, we can affirm that the production of entropy per unit of time represents a physical quantity to evaluate cancer's complexity as well as robustness, namely the ability of a system to continue functioning in the face of internal or external perturbations or fluctuations.

Landau's seminal work (Landau & Lifshitz 1964) proposed a theory of continuous phase transitions in which symmetry breaking occurs near the critical point. In correspondence with the formalism proposed by Landau, a potential function is defined Φ, known as the Landau potential. The Landau potential Φ is defined in terms of the state variables that characterize the system, for example, temperature and pressure, as well as a function of the so-called order parameter η, which is empirically defined.

To formalize out-of-equilibrium phase transitions, a term we coined as biological phase transition (Betancourt-Mar *et al.* 2017), during the emergence and evolution of cancer, we selected the dissipation function, $\Psi \equiv T\dot{S}_i$, which is a non-equilibrium thermodynamic potential as an analogy to the Landau potential Φ.

Thus, we have that, in the case of the emergence and evolution of cancer, biological phase transition is selected as an order parameter η, the difference between the fractal dimension of healthy cells D_f^H and the fractal dimension of tumor cells D_f^T, such that:

$$\eta = D_f^H - D_f^T \text{, (27)}$$

Thus, we have that at the critical point P_C it holds that $\eta = 0$ and so on in any other "ordered" phase $\eta \neq 0$. In this way, the order parameter η is called the degree of complexity (Betancourt-Mar *et al.* 2017).

Considering Eqs. (27) and (26), and making a power series expansion of the dissipation function Ψ, assuming for simplicity that $D_f^H = 1$, is obtained

$$\Psi\left(\dot{\xi}, d_f^C\right) = \Psi_0\left(\dot{\xi}, d_f^C\right) + \alpha\left(\dot{\xi}, d_f^C\right)\eta^2 + \beta\left(\dot{\xi}, d_f^C\right)\eta^4 \text{ , (28)}$$

Eq. (28) represents an out-of-equilibrium extension of Landau's Theory and allows formalizing biological phase transitions through non-equilibrium thermodynamics. In this way, we understand how the development of a primary tumor from a microscopic level—an avascular growth—to a macroscopic level—the vascular phase—and the subsequent appearance of metastases do not occur simply by accumulation of malignant cells but through bifurcations, i.e., a biological phase transition (Izquierdo-Kulich *et al.* 2013; Llanos-Pérez *et al.* 2015; Llanos-Pérez *et al.* 2016; Martin *et al.* 2017; Betancourt-Mar *et al.* 2017; Guerra, A, *et al.* 2018; Betancourt-Padron *et al.* 2020; Nieto-Villar & Mansilla 2021).

Conclusions and Remarks

In summary, non-equilibrium thermodynamics and nonlinear dynamics articulate coherently. This let us establish a formal path of what could become the thermodynamics of complex processes. As essential aspects, it was shown that:

1. On the one hand, the entropy production rate is a physical magnitude representing a Lyapunov function *per se*, regardless of whether the dynamic system is close to or far from equilibrium, constituting an extremal criterion.
2. Conversely, the entropy production rate constitutes a complementary method to the sensitivity analysis of differential equations and appears as a non-extremal criterion.
3. An extension of the formalism to biophysical-chemical systems, on the one hand, shows the use of the dissipation function as a non-equilibrium thermodynamic potential in the characterization of biological phase transitions.
4. On the other hand, it was evidenced that the rate of entropy production represents a physical magnitude useful to evaluate the complexity and robustness of cancer and it may be used as a quantitative index of the metastatic potential of tumors.

Appendix: Lyapunov Function

Let the dynamical system be defined by:

$$\begin{bmatrix} \frac{dx_1}{dt} \\ \vdots \\ \frac{dx_n}{dt} \end{bmatrix} = \begin{bmatrix} f_1(x_1, \dots, x_n) \\ \vdots \\ f_n(x_1, \dots, x_n) \end{bmatrix} \qquad (1)$$

where the functions $f_1, \dots f_n$ are assumed to be continuous and have continuous first-order partial derivatives with respect to all variables $x_1, \dots, x_n$. Let us further suppose that:

$$f_i(0, \dots, 0) = 0 \quad ; \quad i = 1, \dots n$$

That is, the origin of the coordinates $(0, \dots, 0)$ is an equilibrium position of the system.

It is said that the function $V(x_1, \dots x_n)$ is a Lyapunov function for the equilibrium position of the system if:

a) $V(x_1, \dots x_n)$ is continuous in a neighborhood $\mathfrak{V}$ of the point $(0, \dots, 0)$, as well as all its first-order derivatives with respect to the variables $x_1, \dots, x_n$. Further:

$$V(x_1, \dots x_n) \geq 0$$

in the neighborhood $\mathfrak{V}$ of the point $(0, \dots, 0)$.

b) The derivative concerning the system (1):

$$\frac{d}{dt} V\big(x_1(t), \dots x_n(t)\big) = \sum_{i=1}^{n} \frac{\partial}{\partial x_i} V\big(x_1(t), \dots x_n(t)\big) \frac{d}{dt} x_1(t) < 0$$

where $\big(x_1(t), \dots x_n(t)\big)$ is a trajectory of the system (1).

Notice that:

$$\sum_{i=1}^{n} \frac{\partial}{\partial x_i} V\big(x_1(t), \dots x_n(t)\big) \frac{d}{dt} x_1(t) = \langle grad\, V\big(x_1(t), \dots x_n(t)\big), [f_1, \dots f_n] \rangle$$

That is, the scalar product of the gradient of the function $V(x_1, \dots x_n)$ evaluated in the trajectory $\big(x_1(t), \dots x_n(t)\big)$ of the system and the vector field of the system evaluated in the same trajectory:

$$[f_1, \dots f_n] = \big[f_1\big(x_1(t), \dots, x_n(t)\big), \dots, f_n\big(x_1(t), \dots, x_n(t)\big)\big]$$

The fact that this scalar product is less than zero indicates that the angle between the vector $gradV$ and $[f_1, \dots f_n]$ must be bigger than 90°. This condition guarantees the asymptotic stability of the equilibrium position $(0, \dots, 0)$.

Figure 1 shows what was previously described for the case of $n = 2$.

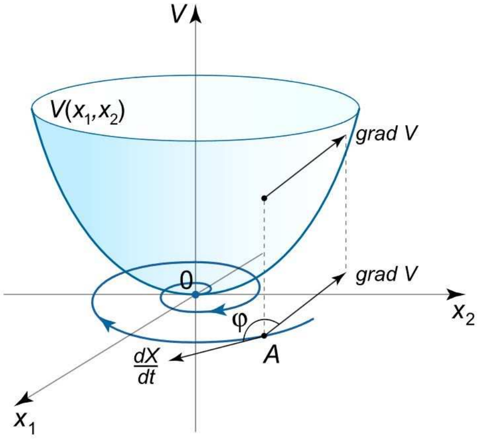

Figure 1

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