Research Article
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On the relationship between aging & cancer

Abstract

This work discusses the relationship between the biological aging and cancer in a unified approach from the perspective of thermodynamics. Taking calorimetric data from some published studies on normal and altered by metastatic carcinoma human metabolism, it is calculated the entropy production rate. It is observed that the entropy production rate in normal individuals decays with age, and develops a kind of first order phase transition. In metastatic carcinoma patients, we observed a similar tendency of decay with age; but metastatic carcinoma patients showed a larger entropy production rate than healthy humans. This can be interpreted in terms of a cancer higher robustness in metastatic phase. Furthermore, it is shown that the entropy production rate per surface area as a function of chronological age can be considered as a Lyapunov function. So, the entropy production per unit time could be considered as a physical marker of biological age and a predictor of longevity.

Keywords: aging, cancer, metabolic rate, entropy production rate, biological age

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Abbreviations: SDAT, senile dementia–alzheimer type; ROS, reactive oxygen species; DNA, deoxyribonucleic acid; OxPhos, oxidative phosphorylation

Introduction

Longevity and aging are still one of the most fascinating topics of human knowledge. Despite all the achievements in molecular biology and genomics, the mechanism for aging processes is still greatly unknown. There are several theories of aging. In 1990, an excellent review by Mevdevev,[1] indicated that there were more than 300 theories of aging and the number is increasing.[2–5] There is consensus today that aging processes are multifactorial and complex, which constitutes the main difficulty in reaching a single approach or theory. Lopez-Otin et al.[6] identify and categorize the cellular and molecular hallmarks of aging and propose nine candidate hallmarks that are generally considered to contribute to the mammalian aging processes and together determine the aging phenotype: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. In general, the theories of aging can be grouped into three major groups:

1. Those related to the action of reactive oxygen species, ROS.[7,8]
2. The theories that establish a link between metabolic rate and the longevity of organisms.[9]
3. Those that focus on the aging process from a thermodynamically point of view.[10–14]

According to the theory by Harman[7] the main factor that induces the aging processes is the deleterious action of free radicals on biopolymers. The main portion of the oxygen used by the aerobic organisms is converted to water. However, some enzymes such as triptofan-oxigenasa, and the xanthine-oxydase, can catalyze oxidative reactions by transferring one electron from the substrate to each oxygen molecule, generating mainly free radicals such as radical superoxide, hydroxyl radical and hydrogen peroxide and so on (ROS).[8]

The ROS can react in several ways; e.g., acting on a stable molecule, can produce another one radical in a complex network of reactions. This causes the oxidation of unsaturated fatty acids and phospholipids from biological membranes and the generation of by-products such as aldehydes, and hydrocarbons as methane and ethane. Free radicals are too able to react with nucleic acids, DNA, proteins and polysaccharides,[15] disturbing the cellular normal functions

According to the theory given by Sohal,[9] the rate of aging and metabolic rate of organisms are inversely correlated. Effects of metabolic rate on aging may be mediated by ROS. Antioxidant defences tend to decline during aging, whereas, the ROS induced damage appears to increase with age.

These two approaches are closely related, and both consider several facts including how the aging is operating through the degenerative diseases, such as, cardiovascular disorders, cancer, atherosclerosis, diabetes, Alzheimer dementia (SDAT), and so on.[16–18] It leads to progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death. The incidence of all of these diseases increases rapidly with aging (in the case of cancer, the increasing is remarkable fast).

Cancer is the generic name given to a complex network of interactions of malignant cells which have lost their specialization and control over normal growth. This network of malignant cells could be considered as a nonlinear dynamical system, self-organized in time and space, far from thermodynamic equilibrium, exhibiting high complexity, robustness and adaptability.[19]

In general, biological systems can be considered as complex dynamical systems that are self-organized far from the thermodynamical equilibrium. Complexity and diversity of these systems are the main features that have lead to find a multi-factor theory for aging.

A great step in the understanding of the complexity of the biological systems was given by Prigogine.[20] Dissipative structures are able to self-organize themselves far from the thermodynamical equilibrium, and emerge as a consequence of processes that operate in the threshold of the instabilities of stationary states, maintaining its

structure by dissipating toward the environment. Those structures are observed by hierarchical ordering on the matter.

The complexity of the biological systems confers themselves robustness[21] and represents a purposeful factor that enables capacity to perform specific actions and functions. From this point of view, complexity and diversity in biological systems are results of self-organized forms and represent qualitative features of them.

The third group of theories on aging, no less important than the two other ones, has oriented the study of aging process from a thermodynamic point of view.[10–14] Despite of not enjoy the same popularity as the formers, this approach provides much essential information. Only a systems analysis approach can offer an integrated picture of a phenomenon as complex and multifaceted as aging. Furthermore, a thermodynamical systems viewpoint may be useful for theory testing, since the adequacy of a postulated mechanism of aging is best judged by its compatibility with senescent changes.[10]

The main purpose of the present work is to discuss the relationship between the biological aging and cancer, with a unified approach using the thermodynamic point of view. The manuscript is organized as follow: In Section 5 is presented the methodology of work; theoretical framework based on thermodynamic formalism, particularly the entropy production rate due to metabolic rate for healthy humans and patients with metastatic carcinoma. In Section 6 the results and the discussion are presented. Finally, some concluding remarks are presented in section 7.

The methodology of work

The development of the complex systems theory,[22] systems biology[23] and thermodynamics of irreversible processes[20] made possible to widen the scope of the study of biological systems. For example, those observations that show an age-related loss of complex variability in multiple physiologic processes including cardiovascular control, pulsatile hormone release, and electroencephalographic potentials.[24–26]

Fenninger & Mider[27] observed unexplained elevation of the basal metabolic rate in some patients with cancer. 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.[28] The regulation of metabolism, relevant to senescence process,[29] would be a key to improve as well as to identify new anti-cancer therapies in the future.

Thermodynamic framework of the aging process for the biologic systems permits us to see this problem as a whole, taking into account that the "whole" is more than the sum of its parts. As emphasized in the introduction, a thermodynamical systems viewpoint may be useful for theory testing, since the adequacy of a postulated mechanism of aging is best judged by its compatibility with senescent changes.[10] Moreover, in previous works,[19] we have shown how the thermodynamic formalism, allows to evaluate the evolution, robustness and complexity of cancer.

We can ask too basic questions about aging, which would allow us to approach the issue:

1. How to explain the onset of the aging process for the human species?
2. How to explain the emergence of degenerative diseases, in particular, cancer?

As we know from classic thermodynamics, if the constraints of a system are the temperature T and the pressure P, then the entropy production can be evaluated us ing Gibbs's free energy,[30] (see formula (1)). If the time derivative of (1) is taken, we obtained the entropy production rate (see Formula (3)); where $\frac{\delta S_i}{dt}$ represents the entropy production rate, $\dot{S}_i$ The term $\frac{dG_{Tp}}{dt}$ can be developed by means of the chain rule as a function of the degree of advance of the reaction $\dot{\xi}$ (see formula (3)); where $\left(\frac{\partial G}{\partial \xi}\right)_{TP}$ according to De Donder & Van Rysselberghe[31] represents the Affinity $A = -\left(\frac{\partial G}{\partial \xi}\right)_{TP}$ and the term $\frac{d\xi}{dt}$ is the reaction rate. $\dot{\xi}$ Using the expression for the Gibbs free energy, G=H–TS, we obtain, formula (4). The term $\left(\frac{\partial H}{\partial \xi}\right)_{TP}$ represents the heat of process r . Sometimes it is possible to neglect the term $\left(\frac{\partial S}{\partial \xi}\right)$ due to $\left|r_{Tp}\right| \gg \left(\frac{\partial S}{\partial \xi}\right)_{TP}^{Tp}$ [32]Taking into account (3) and (4), we get that the entropy production rate can be rewritten as (see formula (5)). The formula (5) is an approximation to determine the entropy production rate of a living organism.[32] The equation (5) can be rewritten according to Zotin[33] using the metabolic rate as follows (see formula (6)); where $\left(\frac{\delta q}{dt}\right)_{Tp} \equiv \dot{q} = \dot{q}_{o_2} + \dot{q}_{GI}$, are the metabolic rate of oxygen Consumption $\dot{q}_{o_2}$ because of oxidative phosphorylation (OxPhos) and due also to glycolysis $\dot{q}_{GI}$, respectively. Under aerobic conditions $\dot{q}_{GI}$ is negligible, except for cancerous cells where the glycolysis is the main process.[34] although the significant increase of glycolysis rate in tumors has recently been verified, yet few oncologists or cancer researchers understand the full scope of Warburg's work[35] despite of its great importance.

For healthy humans, the rate of entropy production S_i can be determined from the formula (7); where $\dot{q}_{GI}$ related to metabolic rates for different individuals and is determined under mental and physical resting as complete as possible using pleasant room temperature and 12-14 hours after the last meal; the term $\dot{q}_{GI}$ related to the glycolysis process is negligible under aerobic conditions.

$$\delta s_i = -T^1 dG_{Tp} \quad (1)$$

$$\frac{\delta S_i}{dt} = -\frac{1}{T}\frac{dG_{Tp}}{dt} \quad (2)$$

$$\frac{dG_{Tp}}{dt} = \left(\frac{\partial G}{\partial \xi}\right)_{Tp}\frac{d\xi}{dt} \quad (3)$$

$$A = -\left(\frac{\partial H}{\partial \xi}\right)_{Tp} + T\left(\frac{\partial S}{\partial \xi}\right)_{Tp} \quad (4)$$

$$\frac{\delta S_i}{\partial t} = \dot{S}_i = \frac{1}{T}A\dot{\xi} \approx \frac{r_{Tp}\dot{\xi}}{T} = \frac{1}{T}\left(\frac{\delta q}{dt}\right)_{Tp} \quad (5)$$

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$$\dot{S}_i = \frac{\dot{q}_{o_2} + \dot{q}_{GI}}{T} \quad (6)$$

$$\dot{S}_i \approx \frac{\dot{q}_{o_2}}{T} \quad (7)$$

$$\dot{S}_i = f(\Omega) > 0 \quad (8)$$

$$\frac{dS_i}{dt} = \frac{\partial S_i}{\partial \Omega} \cdot \frac{d\Omega}{dt} \leq 0 \quad (9)$$

Results and discussion

In Figure 1 is shown the rate of entropy production per surface area $\dot{S}_i$ (see formula (7)) for the healthy humans under basal conditions for both sex and different age. For calculations, the data reported by Boothby[36] was used.

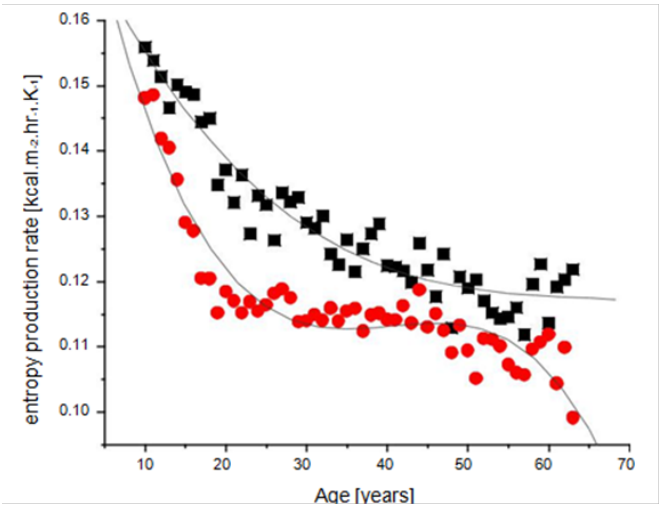

Figure 1 The rate of entropy production per surface area, $\dot{s}_i$, for the healthy humans under basal conditions for both sex (black points-male, red points-female) and different age.

For both sex it was obtained the polynomial regression: $\dot{S}_i = a + b\Omega + c\Omega^2 + d\Omega^3$ where Ω represent the age and the constants are: for male (a=0.178±0.006,b= -0.0027±0.0006,c=4E-5± 2E-5,d = –2E-7 ± E-7; R-square =0.91564, SD=0.00344, N=54,P<0.0001); and for female (a = 0.194±0.006,b= -0.0062±0.0006,c =1.6E-4±2E-5,d= –1.3E-6 ±2E-7;R-square=0.88505,SD=0.00349,N=54, P<0.0001).

The polynomial regression, reminds the van der Waals equation of state,[37] which it is useful to describe the first order phase transitions. As can be seen (Figure 1), aging processes are activated for both sexes about the 20 years old in a kind of first order phase transitions. This is coincident with what is already accepted in the literature.[38]

It is obvious that these calculations are approximations. But the trend starting from the 20-years-old age clearly shown that the aging processes begin to be activated and hence the bio systems are more sensitive to perturbations. Experimental facts indicate this trend. For example, the breathing capacity of the human being is optimal and begins to decline, curiously, after the twenty years age.[39] Moreover, it has been pointed out in the literature[25] that the complexity of the cardiac rhythm changes with the age of the healthy individual going from more complex electrocardiograms to other ones simpler and, finally, to the periodical ones. It has also been seen in heart diseases patients.[26]

This evidence, gives us a plausible response to the emergence of aging processes, and allows us to postulate that they are activated through what it could be called "biological phase transition". Furthermore, although the human males exhibit greater complexity ($> \dot{S}_i$) than to the females ones, which implies greater robustness,[40–42] it is observed that slope in healthy females from 20 to 50 years, is lower than that of males (Figure 1). It gives some stability and also robustness during the active period of the women.

Starting from about the 50 years, women undergo a drastic reduction of its complexity, i.e. become less robust. Curiously, it is known that during these ages the women experience strong hormonal changes, particularly menopause that accelerates the aging processes.[43–45]

Generally, it is seen that with increase of age, the entropy production rate decreases, i.e., decreases the complexity, as other authors have pointed out.[46]

In a previous work[47] we have shown that the rate of entropy production is a Lyapunov function, in fact we extended this formalism to the development of cancer.[41,42,48–50] Thus we have the entropy production per unit time meets the necessary and sufficient conditions for Lyapunov function,[51] see formula (8); where Ω is the vector of control parameters. In this case, we take the age of the subjects as the control parameter (Ω ≡ chronological age). The Eulerian derivative (8) must hold (see formula (9)).

Since, as it is natural, Ω is related with chronological age, $\frac{d\Omega}{dt} > 0$, then it fulfills that: $\frac{\partial \dot{S}_i}{\partial \Omega} \leq 0$, which can be demonstrated from Eq. (8) and also shown in Figure 1. That allows us to affirm that the rate of entropy production is a Lyapunov function, i.e., shows the directional character of the aging process.

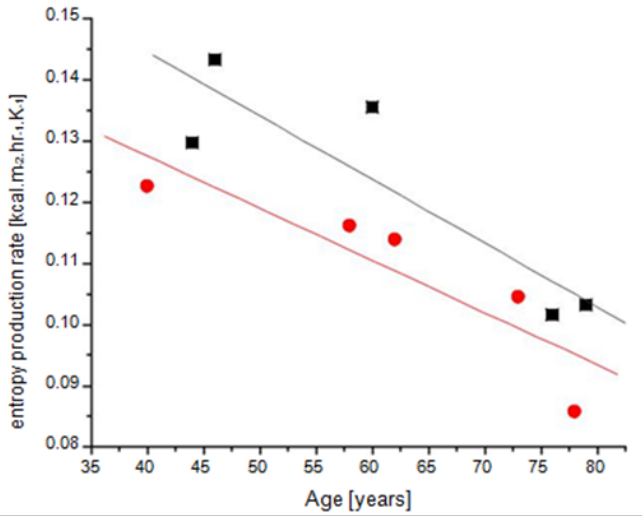

Figure 2 The entropy production rate per surface area S_i for the patient with metastatic carcinoma for both sex (black points-male, red points-female) at different ages.

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We arrive by this way of thinking that the activation of the aging processes occurs on a natural way for the biosystems. This conjecture is according to the theory given by Cutler[52–54] where each mammalian species is characterized by a particular lifespan. Physiological and psychological changes that occur by aging have shown to indicate the biological age of the individual.[55]

In relation to the second aspect: how to explain the emergence of the degenerative diseases? According to the Harman theory[56] of free radicals, these species, ROS, are generated by chain reactions and are present in the onset of the degenerative diseases such as cancer, atherioesclerosis, etc. In the theory given by Sohal,[57] the rate of aging and metabolic rate of organisms are inversely correlated. Effects of metabolic rate on aging may be mediated by ROS. Antioxidant defences tend to decline during aging, whereas, the ROS induced damage seems to increase with age.[58]

Here is precisely established the link between the present thermodynamic framework and the Harman and Sohal theories.[7,9] In particular in cancer, it is well known the significant increase of glycolysis rate observed in tumors.[28,34]

Consequently, for cancer we need to add the term related to the entropy production due to the glycolysis $\dot{q}_{GI}$ to Eq. (7) as it is in the Eq. (6). To evaluate the entropy production rate for cancer patients, we use data of the caloric expenditure report by Holroyde et al.[59] for patient with metastatic carcinoma.

Figure 2 shows the entropy production rate per surface area, $\dot{S}_i$, for the patients with metastatic carcinoma for both sex and different age.

In the patients for metastatic carcinoma, we observed a phenomenological tendency like that of healthy people (Figure 1). On the other hand, the complexity decreases with age for both sex and in the case of males is observed higher complexity compared to females.

Figure 3 shows the entropy production rate per surface area $\dot{S}_i$ for both sexes (left-female, right-male) for the healthy humans and cancer patients, taking the same ages for both healthy and diseased.

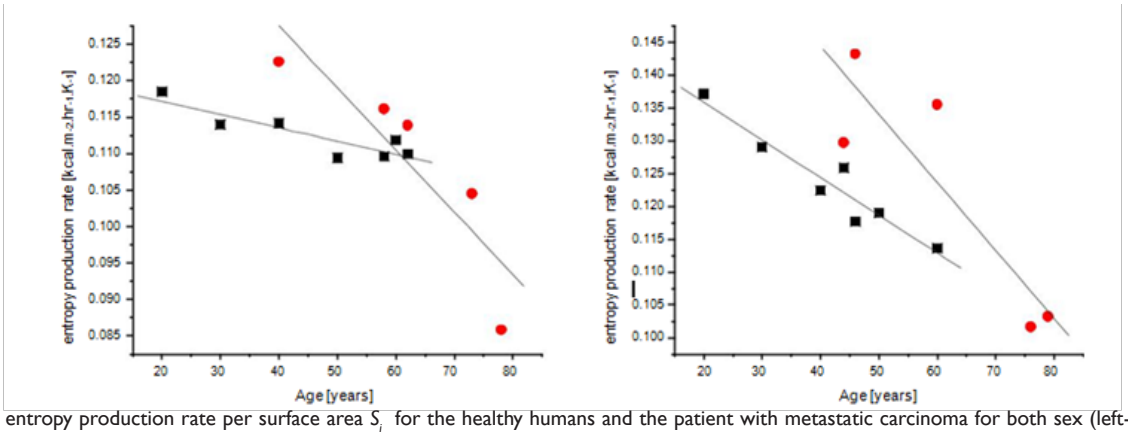

Figure 3 The entropy production rate per surface area $\dot{S}_i$ for the healthy humans and the patient with metastatic carcinoma for both sex (left-female, right-male), (black points-cancer, red points- health) at different ages.

If we compare the healthy individuals with patients of both sexes for the same chronological age, we observe that people with cancer exhibit greater value the entropy production rate, which can be interpreted as that the cancer exhibits a higher robustness, an aspect that we have found in previous works.[40–42] Moreover, these results give a plausible explanation to the unexplained elevation of the basal metabolic rate that has previously been reported for cancer patients.[27,60]

Conclusions and remarks

As point out by Strehler,[61] who defines aging by means of four postulates, we could add a fifth one: the aging is a complex network of interactions that could be considered as a nonlinear dynamical system, self-organized in time and space, far from thermodynamic equilibrium, exhibiting high complexity, robustness and adaptability, whose functions decline with age.

As has been postulated,[62,63] the dynamics of biological organisms, in their various levels of organization, are not "just" processes, but permanent critical transitions and, therefore, changes of symmetry. The dynamics of symmetries and symmetry breakings provide a new, crucial role for symmetries in biology with respect to physics.

In summary, in this paper we arrive as following theoretical assumptions:

1. The aging processes arises at the age of about twenty years and appear as a kind of first order phase transitions, what it we could call "biological phase transition".
2. We have shown that the entropy production rate per surface area $\dot{S}_i$ as a function of the age of the subjects, with Ω as control parameter, can be considered as a Lyapunov function.
3. The entropy production rate could be considered as a physical marker of biological age and a predictor of longevity.
4. The entropy production rate may provide new ways to monitor senescence and test the efficacy of specific interventions to modify the age-related decline in adaptive capacity.

The current theoretical framework will hopefully provide a better understanding of the aging processes and cancer and contribute to improvements in human health span and longevity and in the cancer treatment.

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Conflict of interest

The authors declare no conflict of interest.

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