Thermodynamic approach to the aging process of biological systems.

S J.M. Nieto-Villar[1*], J. Rieumont[1], R. Quintana[1] & J. Miquel[2]

[1]Physical-Chemistry Department, Faculty of Chemistry, Ave. Zapata and G. Vedado, University of Havana. Havana. 10400 Cuba. *Email: nieto@fq.uh.cu, Fax (537) 802360
[2]University of Alicante, Alicante, Spain

Recibido: 21 de febrero de 2002 Aceptado: 8 de noviembre de 2002

Palabras clave: proceso de envejecimiento, sistemas dinámicos, termodinámica no equilibrada, dinámica oscilatoria
Keywords: aging process, dynamical systems, non-equilibrium thermodynamics, oscillatory dynamics

SUMMARY: Aging process was considered from the thermodynamic point of view. This approach is based on the non linear theory of dynamic systems which permits to study the bio-systems beyond the classical scope and on dissipative structures. Several oscillating and chaotic chemical systems were studied using the rate of entropy production as an extension of the thermodynamics of irreversible processes to chemical systems far from the equilibrium. Calculations of rates of entropy production in human beings have confirmed the hypothesis that stable evolution of bio-systems may occur through a chaotic dynamic state. Thus, periodic or quasiperiodic oscillations may emerge as a natural way and then can be postulated that aging process begins. The system becomes more sensitive to perturbations, increasing the damages and leading to degenerative diseases.

INTRODUCTION

Factors that determine aging (We are not referring to the social aspects, way of life, etc.) constitute in the present one of the fundamental problems of the human knowledge. The multi-factor nature of aging is the main difficulty to reach a unique approach or theory.

There are several theories [1,2] from which Harman's theory [3] is from our point of view the more plausible because considers several facts and the way aging is operating through the degenerative diseases such as cancer, atheroesclerosis, Alzheimer dementia (SDAT), etc.

According to the free radical theory given by Harman the main factor that induces such diseases 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, are able to 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. Free radicals can react in several ways, for example, acting on a stable molecule can produce another one radical as in a chain reaction.

Thus, oxidation of unsaturated fatty acids and phospholipids from biological membranes is produced disturbing the cellular behavior and producing by-products such as aldehydes and hydro-carbons such as methane and ethane. Free radicals are ableto react with nucleic acids, ADN, proteins and poly-saccharides.[4]

In general a biological system can be considered as a complex dynamic system that is changing 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 comprehension of the complexity of the biological systems was given by Prigogine. [5] Dissipative structures are able to auto-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 energy and mass to the environment. Those structures are observed by hierarchical ordering on the matter. [6]

As examples the well-known Benard's instability in hydrodynamic fluids, oscillating chemical reactions where oscillating intermediary concentrations are coupled with diffusion giving rise to reaction-diffusion patterns and biochemical systems such as the NADH oxidation catalysed by the horseradish peroxidase. [7]

From this approach, complexity and diversity in biological systems are not factors to produce new auto-organization forms but qualitative features of them. This approach also permits to study the biological systems and their auto-organization as as a whole independently of the particular features and complexity. Complexity is a functional factor that enables to the system perform specific actions.

On the other side the physico-mathematical development of the theory of non-lineal dynamics [8] made possible to widen the scope of the study of biological systems. It has been found that "normal" regulation and control systems such as the nervous system and cardiac rhythm present a chaotic dynamics.

The main purpose of the present paper is to discuss the biological aging with a unified approach using the thermodynamic point of view. This approach is based on the theory given by Prigogine about dissipative structures combined with the non-lineal dynamics.

In Section 2 an overview of the dynamic systems is offered and in Section 3 a thermodynamical approach to the biological systems using as models oscillating and chaotic chemical reactions and an extension of the evolution criterion for these systems far from the equilibrium. Finally, in Section 4 is discussed the aging of the biological systems and a conjecture about the thermodynamical approach.

NON-LINEAL DYNAMIC SYSTEMS

The purpose of this section is to offer an overview about the fundamental concepts of the theory of dynamic systems and its impact on the study of the biological systems. There is a specialized review on this matter that the reader can use to get a better insight in this topic. [9,10] .

Dynamic systems. Concept

In the classification of dynamic systems are considered every physical, chemical, biological or meteorology system. Qualitative features of every non-lineal dynamic system during its evolution as a dissipative system are described by the solutions of the ordinary differential equation.

$$\frac{dX_i}{dt} = F_i(\boldsymbol{X}, \mu) \qquad (2.1)$$

On the phase space $\Re^m$ of dimension **m** the vector $\boldsymbol{X}$ represents the coordinates that describe the system (for example concentration of chemical species, etc.); μ is the vector of control parameters and its variation determine the qualitative behavior of the system dynamics and F_i is a non lineal function of concentrations, differentiable and depends on μ.

Solutions $\phi(X, \mu)$ of equation 2.1 can be describe by the action flow F^t. If the system is dissipative, that are those physically important, the divergence of the flow $\nabla.F^t$ is negative. This means that the flow in the phase space shrinks during its temporal evolution.

Thus, for $t \to \infty$ the initial finite volume V (commonly known as Lebesgue's dimension) of R^m in the subspace A of finite volume in a dimension D smaller so that $D < m$. For a dynamic system under chaotic regime D is a whole number usually known as fractal dimension (D_F).

Ensemble A is called an attractor if the trajectory with initial condition $X_o \in V$ can be attracted to a compact set of points A in the phase space.

For simple attractors such as fixed points (steady state) or periodic orbits (limit cycle, torus) the orbit $X(t)$ is stable if in the vicinity Ω all points contained in the orbit approach asymptotically to Ω. On the contrary if at least one point is moving away the orbit is unstable.

Attractors that are originated by aperiodic oscillations are chaotic. Thus, shapes of high complexity in the phase space arise and were called fractals by Mandelbrot. It must be noted that volume shrinkage does not occur in all directions, in fact the trajectories in some directions are moving exponentially away and others are attracted. Thus, the dynamic behavior is extremely dependent on the initial conditions.

Under chaotic regime the system shows a high complexity and is generating new information, as a consequence the forecast of new states is forbidden.

Changes on the dynamics of the system are ruled by the control parameters. In this case the "phase transitions" are produced by a bifurcation. If a bifurcation takes place the attractor becomes unstable and the system moves towards a stable state and a new self-organization emerges. Bifurcations can be classified according to how stability is lost, for example, en dependence of what invariant exists in the phase space before and after bifurcation. [11]

In general the global stability of a system during its evolution can be evaluated through the Lyapunov function **V**. [12] It is defined as a function of **n** variables $V = V(X_1,...,X_n)$ that satisfies around the beginning of the coordinate axis the following conditions:

1. $V > 0$ only if $X_i = 0 \quad \forall\, i = 1, ..., n$.

The eulerian derivative

$$\frac{dV}{dt} = \sum \frac{\partial V}{\partial X_i} \cdot fi(t, X_1, ..., X_n) \le 0$$

when $t \ge t_o$ then is said that the state is asymptotically stable.

Evolution towards a chaotic regime is the result of a "cascade" of bifurcations. Several ways to attain chaos has been identified [12] such as period duplicating, intermittence, etc.

Another fundamental feature of a chaotic regimen is its stability in front of external perturbations. A remarkable difference exists with respect to other self-organized stages because the attractor does not change.[13] This is of interest for the biology as was already pointed out because the nervous impulse of the cardiac rhythm in normal Health State are chaotic.[8] In this regime the system exhibits a high complexity due to the generation of new information.

The characterization of the chaotic regime can be done taking into account static properties of the attractor, as the fractal dimension, or

dynamic ones such as the Lyapunov exponents spectrum, the entropy or an stochastic description known as symbolic dynamics.

Attractor dimension

As a consequence of the continuos expansion and contraction of the flux F^t in the attractor A its shape resembles an ameba. The geometric characterization of the set of points in the phase space is called fractal dimension D_F of A, so that is less than the **m** dimension of the phase space and is not an integer. Physically the atractor dimension indicates the number of independent variables that characterize the dynamics of the system.

In general three types of dimensions can be distinguished [14] the topological dimension D_T, the fractal dimension D_F and the information dimension D_I so that $D_T \leq D_I \leq D_F$. Mainly we will talk about the information dimension.

Make to latex around to attractor of like form that we will designate you like "box" to each division of the latex. If **n**(r) is the number of boxes with a probability different from zero and the empty boxes are designed by **i** then pi (r) is the probability of occurrence of the i^{th} box. The ensemble {pi(r)} referred as the probability distribution of resolution **r** (coarse grained), the information contained in the measurement **n** is

$$I(r) = -k\sum_{i=1}^{n(r)} p_i(r)\log p_i(r) \qquad (2.2)$$

where k is a constant, if k = 1/log 2 them unit of $I(r)$ are a bit (binary unit), if $k = k_B = 1.38\times10^{-23}$ J/K (k_B is the Boltzman constant) them the unit are the same as the thermodynamical entropy, such as J/K.

If **r** increases a more refined sequence is generated. Thus, the information dimension represents the speed to which the information scales, as the precision of the measurement, increases

$$D_I = \lim_{r\to\infty}\frac{I(r)}{r} \qquad (2.3)$$

If the probability of all the boxes is the same then $I(r) = \log n(r)$ and the information dimension is reduced to the fractal dimension that was historically called Hausdorff dimension and defined as

$$D_F = \lim_{r\to\infty}\log\frac{n(r)}{r} \qquad (2.4)$$

Lyapunov exponent spectrum

The Lyapunov exponent spectrum represents for a dynamical system the gain and/or loss of means information during its evolution. According to the sign of the exponent the flux F^t for the system is physically characterized. Thus, we have

$$\varepsilon(t) = \nabla . F^t = \varepsilon e^{\lambda t} \qquad (2.5)$$

where $\varepsilon(t)$ is the divergence of the flux F^t and λ is the mean speed of the divergence.

If λ is negative, two close trajectories will converge, in other words the system is gaining information; if λ is zero the trajectories will diverge linearly and finally if λ is positive the trajectories will diverge exponentially losing information in an exponential way during its evolution.

A dissipative system described by $x \in R^3$ is characterized by three Lyapunov's exponents. According to the sign of them the evolutive regime can be classified as: fix point (steady state) if the three exponents are negative, a limit cycle will result for the particular case when one of them is zero; a torus T^2 if two of them are zero and finally a chaotic regime if at least one of them is positive.

There are several ways to define mathematically the Lyapunov's exponents. [15] We will use the mathematical definition that geometrically gives the physical meaning of them.

In a phase space **m** dimensional, the Lyapunov's exponent of the axis **n** is defined as

$$\lambda_i = \lim_{t\to\infty}\frac{1}{t}\log\frac{L_i(t)}{L_i(0)} \qquad (2.6)$$

where Li is the radio of the ellipsoid (flux F^t) along i^{th} axis at time t.

Entropy

Entropy for the dynamical systems has the same physical meaning that the entropy defined by the second law of the Thermodynamics. A detailed discussion of this matter will be offer in Part 3. Here we will define the entropy as the measure of the uncertainty during the evolution of a dissipative system or the degree of information of the system. [11] In this way information and entropy can be measured in the same units, both are positive magnitudes and different from the energy. Thus, information is defined as

$$S(t) = k_B\sum P(\mathbf{x},t)\ln P(\mathbf{x},t) \qquad (2.7)$$

where n(r) and pi(r) have the same meaning as in equation 2.2, **k** is a constant that defines the units of I(r), if k = $1/\log_2 2$ the unit is the bit (binary unit), if k= k_b= 1.38×10^{-23} J/K (k_b is the Boltzman's constant) the units are the same used for the thermodynamical entropy in J/K. Commonly we will use the bit.

The change in time for I(r) in 2.7 when $r \to \infty$ and $t \to \infty$ is known as the Kolmogorov's $\aleph$ entropy (in bits) and is defined as

$$\frac{dI(r)}{dt} \equiv \aleph = \lim_{r\to\infty}\lim_{t\to\infty}\frac{I(r)}{t} \qquad (2.8)$$

Trajectories of a dynamic system can be classified according to the entropy $\aleph$, for $\aleph$=0 periodic oscillations, quasioperidic or steady, for $\aleph$>0 chaotic oscillations and for $\aleph$=∞ noise.

Other important feature of the entropy $\aleph$ is the so-called Pesin's equality [10] defined as

$$\aleph = \sum\lambda^+ \qquad (2.9)$$

where λ_+ is refereed to the Lyapunov's positive exponents. Physically talking $\aleph$ is a measure of the rate of losing information for the system under chaotic regime.

THE THERMODYNAMICS OF DYNAMIC SYSTEM. OSCILLATING AND CHAOTIC CHEMICAL REACTIONS.

Thermodynamics began from the works of Carnot, Clausius, Joule and others at the beginning of the industrial revolution when thermal machines were build. 100 years have elapsed from those machines and now "chemical and biological machines" have chandelled the second law.

One of the tasks today in front of Thermodynamics is to answer to the problems related to the self-organization of the dynamic systems far from the thermodynamic equilibrium. The core of the problem became more clear from the works of Prigogine and his school at the Free University of Brussels in Belgium in the seventieth. Under the name of "dissipative structures" those systems able to self-organize far from the equilibrium as a consequence of the instability of the system and to the continuos dissipation of energy and matter to the surroundings. Professor I. Prigogine was awarded with the Nobel Prize in Chemistry in 1977.

In 1951 the Russian chemist Belousov [16] looking for a solution or culture able to generate some kind of life found the following reaction: In an acidic aqueous solution an organic substance (citric acid) was poured in order to react with an inorganic material (potasium bromate) using a catalyst (cerium IV sulphate) in aerobic conditions. Surprisingly temporal and spatial oscillations due to the intermediary species occurred and reaction-diffusion patterns were observed.

Some years later in 1964 another Russian Zhabotinsky [16] came back to the Belousov's idea and published this reaction that is known at the present as Belousov-Zhabotinsky. Belousov was not alive to know that his idea became a paradigm of the self-organization in chemistry.
Self-organization in chemistry is an ideal model to be used as illustration of the behavior in other hierarchical levels even more complex such as enzymatic reactions, biological cycles, cellular division, etc. [17]

Oscillating and chaotic chemical reaction models

"Chemical cycles" are different from "thermal cycles" because they operate with only one thermic focus while the latter need two according to Carnot so they are a challenge to the Second Law.

We will illustrate our ideas through a series of theoretical oscillating and chaotic chemical reaction models, which have been thoroughly discussed in the literature from the point of view of dynamics. [18,19]
Autocatalator model [19] is shown

$$A \rightarrow x \quad \text{(A-1)}$$
$$x \rightarrow y \quad \text{(A-2)}$$
$$x + 2y \rightarrow 3y \quad \text{(A-3)}$$
$$y \rightarrow B \quad \text{(A-4)}$$

where "y" is autocatalytic generated in the trimolecular step (A.3).
Another well known model is the Brusselator: [17]

$$A \rightarrow x \quad \text{(B-1)}$$
$$B + x \rightarrow y + D \quad \text{(B-2)}$$
$$y + 2x \rightarrow 3x \quad \text{(B-3)}$$
$$x \rightarrow E \quad \text{(B-4)}$$

in which the trimolecular step (B.3) is autocatalytic. The Oregonator is another well-known model [20] developed for the Belousov-Zhabotinsky reaction. [16] Its details are shown:

$$A + Y \rightarrow x + P \quad \text{(O-1)}$$
$$x + Y \rightarrow 2P \quad \text{(O-2)}$$
$$A + X \rightarrow 2x + z \quad \text{(O-3)}$$
$$2y \rightarrow A + P \quad \text{(O-4)}$$
$$Z \rightarrow fy \quad \text{(O-5)}$$

in this case there are three intermediaries x, y and z and two autocatalytic bimolecular steps (O.2), (O.3). Finally as a model for a chaotic reaction we will analyze the model given by Rössler. [21] This model shows some exotic behaviors such as periodic, quasi-periodic and chaotic oscillations and we will see a phenomenon very interesting known as "crisis". [6] The mechanism is the following:

$$A + X \rightarrow 2x \quad \text{(R-1)}$$
$$x + Y \rightarrow 2y \quad \text{(R-2)}$$
$$B + Z \rightarrow 2z \quad \text{(R-3)}$$
$$C + Y \rightarrow D \quad \text{(R-4)}$$
$$x + Z \rightarrow E \quad \text{(R-5)}$$

Details for the rate parameters, initial conditions and control parameter are shown in Table 3.1.

Rate of entropy production as an evolution criterion

For simplicity these chemical reactions can be considered as an ideal mixture in mechanic and thermal equilibrium. Thus, according to T. de Donder the entropy variation is given by dS_s:

$$dS_s = \delta S_i + \delta S_e \quad (3.1)$$

where δS_e is the entropy flux between the system and the environment and δS_i is the production of entropy during its evolution due to the irreversible processes. The fundamental postulate of the Second Law establishes:

$$\delta S_i \geq 0 \quad (3.2)$$

it is to say that the system goes creating entropy $\delta S_i > 0$. Thus, taking the temporal variation of (3.1) is obtained:

$$\frac{dS}{dt} = \frac{\delta_e S}{dt} + \frac{\delta_i S}{dt} \quad (3.3)$$

that can be re-written as

$$\dot{S}_s = \dot{S}_{flow} + \sigma \quad (3.4)$$

where $\dot{S}_s$ is the rate of entropy of the system, $\dot{S}_{flow}$ is the rate of entropy flux and σ is the rate of entropy production ($\dot{S}_p$). If the system travels through a

stationary state, a periodic or quasiperiodic regimen then $\dot{S}_s = 0$ so that

$$\dot{S}_p = -\dot{S}_{flow} \tag{3.5}$$

Under chaotic conditions then $\dot{S}_s > 0$ so that that

$$\dot{S}_p > \left|\dot{S}_{flow}\right| \tag{3.6}$$

According to the Thermodynamics of Irreversible Processes the rate of entropy production $\dot{S}_p$ [23] is given by

$$\sigma = \sum_i J_i X_i \geq 0 \tag{3.7}$$

where J_i is the generalized flux and X_i is the generalized force. In the present case and without concentration or temperature gradients or external fields for the chemical reaction σ is given by

$$\sigma = T^{-1} A.V \tag{3.8}$$

where T is the absolute temperature in Kelvin, A is the chemical affinity and V the rate of reaction. Thus, according to T. de Donder the chemical affinity is equal to

$$A = -\left(\frac{\partial G_{Tp}}{\partial \xi}\right) = RT \ln \frac{K_c}{\prod (C_{ki})^{\upsilon_{ki}}} \tag{3.9}$$

where G is the Gibbs's potential, ξ the degree of reaction, R the gas constant equal to 8.31 J/mol.K and K_c is the equilibrium constant and C_{ki} and υ_{ki} the concentrations and stoichometric coefficients respectively of reactants and products for the substance 'k' in the 'i' step.
On the other side the reaction rate is

$$\frac{d\xi}{dt} = v = \sum v_i = \sum \left(v_i^{+} - v_i^{-}\right) \tag{3.10}$$

where V_i^{-} and V_i^{-} are the forward and reverse reaction rates for the 'i' step respectively. According to the Mass Action Law V_i is equal to

$$v_i^{+} = k_i^{+} \prod \left(C_{ki(+)}\right)^{\upsilon_{ki(+)}} \tag{3.11a}$$

$$v_i^{-} = k_i^{-} \prod \left(C_{ki(-)}\right)^{\upsilon_{ki(-)}} \tag{3.11b}$$

where $\upsilon_{ki(-)}$, $\upsilon_{ki(-)}$, $C_{ki(-)}$ y $C_{ki(-)}$ are the stoichiometric coefficients and concentrations of products and reactants for the compound 'k' in the 'i' step for the forward (+) and reverse (-) reaction; ki^{-} and ki^{-} are the rate constants.
Taking the equations 3.11, 3.10 and 3.9 and substituting in 3.8 is obtained

$$\sigma = R \sum \left(v_i^{+} - v_i^{-}\right) \ln \frac{v_i^{+}}{v_i^{-}} \tag{3.12}$$

For a periodic or quasiperiodic oscillating regime the mean value of 3.12 is

$$\langle \sigma \rangle_{CL,T} = \frac{1}{\tau} \int \sigma dt \tag{3.13}$$

where τ is the period of oscillation. For the chaotic regime the limit of 3.13 is taken $t \rightarrow \infty$ so that

$$\langle \sigma \rangle_{Ch} = \lim_{t \rightarrow \infty} \left\{ \frac{1}{\tau} \int \sigma dt \right\} \tag{3.14}$$

Table 3.1. Rate parameters (ki) and control parameter values (A,B,P) for the models studied.

Autocatal.	Brusselator	Oregonator		Rössler	
k1 = 1 E-3	k1 = 1 E-1	k+1 = 1.34	k-1 = 1 E+4	k+1 = 1	k-1 = 2.5 E-1
k2 = 1 E-2	k2 = 1	k+2 = 1.6 E+9	k-2 = 2.5 E-5	k+2 = 1	k-2 = 1 E-3
k3 = 2.5 E+9	k3 = 1 E+7	k+3 = 8 E+3	k-3 = 4.8 E+11	k+3 = 1	k-3 = 5 E-1
k4 = 1	k4 = 10	k+4 = 4 E+7	k-4 = 1.6 E-10	k+4 = 1	k-4 = 1
A0 = 0.1	A0 = 10	k+5 = 1	k-5 = 1 E-5	k+5 = 1	k-5 = 1
	B0 = 1 E+3	f {0.5 - 1.5}		B = 16.5	
		P0 {1 E-4 - 1 E-1}		D = E = 0.01	
				A0{0-100}	

Models were analytically and numerically explored. A Gear's algorithm was used for the numerical simulation [22].

Table 3.2. Dependence of <σ> for each model according to the value of its control parameter.

state	Autocatalator		Brusselator			Oregonator		Rössler	
	⟨σ⟩	A	⟨σ⟩	A	B	⟨σ⟩	A	⟨σ⟩	A
SS_i [1]	1.4 E-4	1.0 E-1	-------	-------	-------	1.2 E-2	1.0 E-3	9.9 E+3	75
CL [2]	2.2 E-5	1.9 E-2	10	10	1.0 E+3	7.5 E-4	7.0 E-3	7.7 E+3	54
Chaos	-------	-------	-------	-------	-------	-------	-------	3.4 E+3	30.5
Crisis	-------	-------	-------	-------	-------	-------	-------	1.6 E+2	29
SS_f	3.7 E-6	2.0 E-3	3.0 E-2	7.0 E-1	913	2.6 E-6	2.2 E-2	2.5 E+1	15.7

[1] stationary state, initial (i), and last (f) respectively.
[2] limit cycle, and period doubling.

Discussion

In Table 3.2 are shown the mean values of σ in the attractor during the evolution of the system for each model in dependence of the value of the control parameter.

It is observed how the systems go over different attractors during its evolution in dependence of the control parameter. If the control parameter decreases (as in the case of a reactant) the system decreases its rate of entropy production. For example for the Autocatalator and the Oregonator ($f = 0.5$) is possible to reach a limit cycle due to a Hopf's bifurcation from both stationary states. According to the Second Law, the limit cycle can not be attained from the final stationary state (SS_f) due to the lesser value of <σ>. In fact to the system returns to the limit cycle from SS_f the concentration of the reactant A should increase during the reaction (for the case of the Autocatalator) or decrease the product P for the Oregonator. In both cases it is chemically senseless.

For the Rössler's model the behavior is more complex but like to the other models studied. It is interesting to point out the sudden departure from the chaotic to the stationary state. This phenomenon is not very usual and has been described in the literature as "crisis' [6] for the case when the chaotic behavior is left to pass to periodic oscillations.

From the standpoint of the biologic systems this fact is very curious because if the human being can go through a chaotic regime in some stage of its life, we can ask ourselves. What consequences will result for the system if by changing a control parameter a "crisis" is triggered? Or is actually this the natural way to be choosing for the living systems during its evolution? Or is it the choice of the living system when the degenerative diseases emerge?.

The global stability of the system far from the thermodynamic equilibrium as has been demonstrated in previous works [24] is given by the functional relation of with the control parameters that are capable to change the characteristics of the self-organization of the system. For example for the case of the Oregonator <σ> can be written as a function of P and f, then taken the Eulerian derivative we have

$$\frac{d\langle\sigma\rangle}{dt} = \frac{\partial\langle\sigma\rangle}{\partial P}\cdot\frac{dP}{dt} + \frac{\partial\langle\sigma\rangle}{\partial f}\cdot\frac{df}{dt} \le 0 \qquad (3.15a)$$

if f is a constant, them:

$$\frac{d\langle\sigma\rangle}{dt} = \frac{\partial\langle\sigma\rangle}{\partial P}\cdot\frac{dP}{dt} \le 0 \qquad (3.15b)$$

where P is the reaction product that increases in

$$\text{time}\left(\frac{dP}{dt} > 0\right), \text{ thus } \frac{d\langle\sigma\rangle}{dP} \le 0$$

as is shown in Table 3.2. This means that <σ> is a Lyapunov's function, as was discussed in Part 2, and permits to establish not only the asymptotic stability of the system but according to the Second Law is useful as an evolution criterion.

Equation 3.15 can be written is a more general form for $\mathcal{S}_p = \mathcal{S}_p(\mu)$, where μ is the control parameter vector, thus it should be fulfilled that

$$\frac{d\mathcal{S}_p}{dt} = V,\ \nabla\mathcal{S}_p \le 0 \qquad (3.16)$$

being V the rate vector of μ and $\nabla\mathcal{S}_p$ the gradient of $\mathcal{S}_p$.

FINAL DISCUSSION: PREAMBLE OF A HYPOTHESIS

Thermodynamic approach to the aging process for the biologic systems permits to see this problem as a whole, globally, taking into account that the "whole" is even more than the sum of the different parts.

There are three basic questions to which we must try to answer in order to understand the problem in a first sight:

1. How to explain the beginning of the aging process for different mammalian species?
2. How to explain the appearance of degenerative diseases that cause the aging of biologic systems?
3. How to link the aging theories that exist at the present with this approach?

The first problem to elucidate is the evolution stage through which the biologic systems go (our attention is focused to the human being). A generalized criterion establishes that a stationary state [25] or through several stationary states, the "three stage hypothesis. [26] We shall discuss in detail that point.

Stationary state

There are several definitions about the stationary state from the point of view of the thermodynamics of irreversible process [23] and from the chemical kinetics. [27] As was already discussed in Chapter 3 if a system goes over a stationary state (SS) the following equality must be fulfilled

$$\mathcal{S}_p = -\mathcal{S}_{flow} \qquad (4.1)$$

in order to keep the stationary state.

In such state according to the Prigogine's theorem [17] it is not possible any type of self-organization. Only far from the thermodynamic equilibrium, with increasing of fluctuations to the macroscopic level, the state becomes unstable due to a bifurcation or a cascade of bifurcations thus emerging new self-organization forms. [5]

Thus, the evolution of a biologic system through an SS is not in correspondence with the physical reality observed, these systems are able to self-organize and self-regulation far from the equilibrium. Balmer [28] developed an entropic model for the biologic systems where the entropy rate for the system can change from positive to negative.

From the point of view of the dynamic systems (Part. 2), the equality 4.1 is valid for the stationary states and for the periodic o quasiperiodic regimes. On these stages the Kolmogorov's entropy $\aleph$ is equal to the entropy rate and its value is zero.

According to the above discussion we can guess that the ideal regime for the evolution of the biologic systems is the chaotic one. In such regime suitable conditions are present for the apparition of all kinds of self-organization ways and mechanisms for the self-regulation. Furthermore in such state the system becomes stable to external or internal perturbations, keeping its stability. In this state the system is continuously creating information appearing a "memory" that resembles the evolution picture of the biological species.

Some experimental facts are backing this conjecture. One of them is related to the studies carried out on the human EEG that have shown that the nervous impulse in normal patients is chaotic [29,30] on the contrary in pathologic states such as epilepsy, the dynamics is periodical or quasi-periodical. [31] Another experimental fact is related to the ECG studies where ventricle fibrillation and arrhythmia show a quasi-periodic behavior, it seems that health state are related to chaotic regime.[32] These results permit suggest that the more suitable state for the evolution of a biologic system is the chaotic one.

Rate of entropy production and entropy flow

The entropy flow for the biologic systems (open systems) is given by the equation

$$\mathcal{S}_{flow} = \frac{\sum \mathcal{Q}_i + \sum n\mathcal{C}_i}{T} \qquad (4.2)$$

Where $\sum \mathcal{Q}_i$ y $\sum n\mathcal{C}_i$ are related to the rate of energy and mass changed with the neighborhood. As was shown by Aoki[26]

$\left|\sum \mathcal{Q}_i\right| >> \left|\sum n\mathcal{C}_i\right|$ so that equation 4.2 can be written as

$$\mathcal{S}_{flow} \cong \frac{\sum \mathcal{Q}_i}{T} \qquad (4.3)$$

The body heat $\sum \mathcal{Q}_i$ is lost by radiation and convection (70%), sweat vaporization (27%) and also by breathing, urine and defecation. Thus the entropy flow $\mathcal{S}_{flow}$ is given by the following balance

$$\mathcal{S}_{flow} = \mathcal{S}_r + \mathcal{S}_{cnv} + \mathcal{S}_{evp} \qquad (4.4)$$

where $\mathcal{S}_r$ is the entropy flow due to infrared radiation hat is given by

$$\mathcal{S}_r = \mathcal{S}_{out} + \mathcal{S}_{in} \qquad (4.5)$$

where $\mathcal{S}_{out}$ and $\mathcal{S}_{in}$ are referred as the portion released and absorbed respectively. Thus equation 4.5 can be re-written as

$$\mathcal{S}_r = .\frac{3}{4} A^e \sigma \left(T_s^{\,3} + T_c^{\,3}\right) \qquad (4.6)$$

where A^e is the specific average radiating surface in m^2 m^2(1.52), σ is the Stefan-Boltzman constant equal to 5.67×10^{-8} $J.m^{-2}.\ s^{-1}.K^{-4}$, T_s is the human skin temperature equal to 307.4 K and T_c is the temperature of the calorimeter (surroundings) equal to 303.2 K. Absortivity of the human skin for the infrared radiation is equal to the emisivity according to the Kirchoff Law [33] and its value around unity. Entropy due to the sweat vaporization $\mathcal{S}_{cvp}$ is equal to

$$\mathcal{S}_{evp} = \frac{\mathcal{E}_{evp}}{T_r} \qquad (4.7)$$

where $\mathcal{E}_{evp}$ is the heat released by water evaporation at T_c = 303.2 K and $\mathcal{E}_{evp}$ is equal to 16.8 A^e ($J.s^{-1}$) and T_r is the temperature of the rectum equal to 310.4 K (as a body average). Finally the entropy flow due to convection $\mathcal{S}_{cvp}$ is equal to

$$\mathcal{S}_{cnv} = \frac{\mathcal{E}_{cnv}}{T_s} \qquad (4.8)$$

where $\dot{E}_{cnv}$ is the energy released by convection and is equal to

$$\dot{E}_{cnv} = \dot{E}_{total} - \dot{E}_{evp} - \dot{E}_{rad} = 8.0\, A^{e}\ (J.s^{-1})$$

and T_s is the human skin temperature equal to 307.4 K. Finally the entropy flow due to convection is equal to 8.0 A^e ($J.s^{-1}$).

Thus the net entropy flow is equal to

$$\dot{S}_{flow} = \dot{S}_{in} - (\dot{S}_{out} + \dot{S}_{cnv} + \dot{S}_{evp})$$
$$= 0.170 Jm^{-2}s^{-1}K^{-1}$$

This classical calculation was done by Aoki taking into account the works of Dubois and coll. [26,33,34]. Aoki was able to demonstrate how the surrounding temperature in the interval of 24 to 34°C does not change $\dot{S}_{flow}$. Our purpose was to show how this value was determined in order to use it in further argumentation. However the fact that the flow entropy is constant and independent of the age is a very striking one as has been suggested in the literature. [35]

According to Zotin [36] the rate of entropy production $\dot{S}_p$ can be determined as follows

$$\dot{S}_p = \frac{\dot{Q}_{O_2} + \dot{Q}_{Gl}}{T} \qquad (4.9)$$

where $\dot{Q}_{O_2}$ is the rate of oxygen consumption (metabolic rate) and is related to energy metabolism reflecting the thousands of reactions and physical processes that are occurring in the organism. The term $\dot{Q}_{Gl}$ is related to the glycolysis and is negligible under aerobic conditions. Thus, equation 4.9 can be written

$$\dot{S}_p \cong \frac{\dot{Q}_{O_2}}{T_r} \qquad (4.10)$$

In order to compare the metabolic rates for different individuals and species the rates are determined under mental and physical resting as complete as possible using pleasant room temperature and 12-14 hours after the last meal. Then under these conditions the **basal metabolic rate (BMR)** is obtained.

In figure 1 is shown the data of $\dot{S}_p$ under basal conditions for both sex in dependence of the age of the individual, for calculations the data reported by Ganong [37] was used.

If we compare the $|\dot{S}_{flow}|$ (0.170) with the values for $\dot{S}_p$ for different ages it shown that up to 20 years $\dot{S}_p > |\dot{S}_{flow}|$ so that the entropy rate for the system $\dot{S}_s$ is greater than zero, this fact keeps the biosystem under chaotic regime.

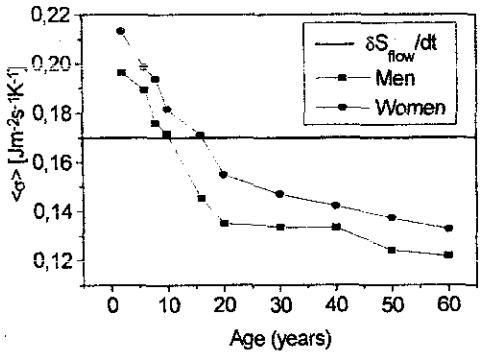

Figura 1. The mean value of the rate of the entropy production under basal conditions for both sex and different age. The dashed line represent the entropy flow.

It is obvious that these calculations are approximately but a trend from the 20 year age is clearly shown; the chaotic regime tends to disappear and the aging processes begin to be activated so the biosystem is more sensitive to perturbations. Experimental facts indicate this trend. Thus, for example, the breathing capacity of the human being is optimal and begins to decline curiously after the twenty years. [38] It has been pointed out in the literature [39] that the complexity of the cardiac rhythm changes with the age of the healthy individual going over the ECG more complex and other ones more simple and finally periodical.

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 [40-42] 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.

To the light of this conjecture, how to explain arising of the degenerative diseases? Besides the oxygen consumption by the organism during the vital processes it occurs a parallel reaction giving the radical-ion superoxide $O2^{\cdot}$. According to the Harman theory [3] of free radicals, these species are generated in chain reactions and are present on the appearance of the degenerative diseases such as cancer, atherioesclerosis, etc.

Here is precisely established the link between the thermodynamic approach and the free radical theory. As a consequence equation 4.10 needs another term due to the entropy production due to the free radical have a hypothesis containing a thermodynamic approach useful to fight against the degenerative diseases that are the main death causation for the third age.

Acknowledgments

We are grateful to the "Ramon Areces" (Spain) Foundation for financial support. An also to British Cooperation Fond.

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