Review

The Gouy-Stodola Theorem in Bioenergetic Analysis of Living Systems (Irreversibility in Bioenergetics of Living Systems)

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Abstract: Thermodynamics studies the transformations of energy occurring in open systems. Living systems, with particular reference to cells, are complex systems in which energy transformations occur. Thermo-electro-chemical processes and transports occur across their border, the cells membranes. These processes take place with important differences between healthy and diseased states. In particular, different thermal and biochemical behaviours can be highlighted between these two states and they can be related to the energy transformations inside the living systems, in particular the metabolic behaviour. Moreover, living systems waste heat. This heat is the consequence of the internal irreversibility. Irreversibility is effectively studied by using the Gouy-Stodola theorem. Consequently, this approach can be introduced in the analysis of the states of living systems, in order to obtain a unifying approach to study them. Indeed, this approach allows us to consider living systems as black boxes and analyze only the inflows and outflows and their changes in relation to the modification of the environment, so information on the systems can be obtained by analyzing their behaviour in relation to the modification of external perturbations. This paper presents a review of the recent results obtained in the thermodynamics analysis of cell systems.

Keywords: entropy; entropy generation; exergy; Gouy-Stodola theorem; irreversibility; living cells; living systems; metabolism; medicine and biochemistry thermodynamics; membrane transport

1. Introduction

Applied thermodynamics is the science which studies both energy and its best use in relation to the available energy resources: energy and energy transformations, including power production, refrigeration and relationships among the properties of matter, including also living matter. Energy is a thermodynamic property of any system. It characterizes any state of a system in relation to a reference state. During any interaction, it changes, but its total amount, in relation to the universe (the system and its environment), is always constant [1], so its physical meaning is related to its variation. Indeed, the useful work is obtained by evaluating the variations of the energy, which means that any change in a system is always related to a transition between two different system states.

The first law of thermodynamics expresses the conservation of energy, while the second law states that entropy continuously increases for the system and its environment [2]. Entropy can sometimes decrease within an open system, but only if it is spent to increase entropy outside the system. The second law highlights that energy has quality as well as quantity and any process occurs with a consequent decrease of this quality [1]. Consequently, applied thermodynamics is a fundamental science for the analysis of open systems when energy transfers and energy transformations occur [1,3].

Nicolas Léonard Sadi Carnot's result on heat engines represents the existence of a readily calculable limit for any rate of conversion of heat into kinetic energy and work [4,5]. The concept of entropy was introduced by Rudolf Clausius [6,7] in order to analyze dissipative processes [6–9]. In 1889, Louis Georges Gouy and, in 1905, Aurel Stodola, independently proved that the lost exergy in a process is proportional to the entropy generation [10–15]. Then, in 1947, Ilya Prigogine and, in 1957, Hans Ziegler proved that a non-equilibrium system develops in the way which attains the minimum entropy production, for Prigogine [16–23], and the maximum entropy production, for Ziegler [24–27], under the existing constraints. Moreover, Prigogine also extended this approach to complex systems in physics, chemistry and biology [10].

In 1982, Adrian Bejan [28–37], introduced the minimum entropy generation approach which is an optimization method for engineering design. Then, he also developed a powerful improvement, named the constructal law. This theory is particularly effective to explain the optimal shapes of natural structures [28]. This law has been used in engineering, economics, physics, biology, hydraulics, geology, in urban designing and physiology, *etc*.

All these approaches describe the internal needs of a system, their optimal paths in the phase space, based on the minimum momentum, *i.e.*, on the least time, but, some complex systems cannot be completely known or described starting from their inside, because there are seldom fully accessible [38–53]. Consequently, for such systems, the use of the previous approaches could be difficult, and it could hold to specific and non-generic models, and the results obtained have been subject of criticism [54]. Last, it has been highlighted that any effect in nature is always the consequence of the dynamic balances of the interactions between the real systems and their environment [55–58]. Energy balances are the results of the exchange of energy between any real system and its environment. The evolution of real systems is always related to a decrease of their free energy, in the least time [59–69].

All these considerations allow us to underline the need of a new approach to complex systems, based on the analysis of the interaction between systems and their environment. This approach can be based just on the Gouy-Stodola theorem, because this theorem, as previously highlighted, allows us to

evaluate the irreversibility and the dissipations in the interaction between systems and their environment, by considering entropy generation, which is related to the exergy lost by the systems during the interactions themselves. Moreover, exergy means available energy, so this theorem can be related to the analysis of the dispersed energy, or to be exact, the exergy lost. Indeed at the beginning of the process, the system could be able to use all the energy, while during the process the irreversibility generates a loss of energy. This approach studies just this lost energy.

Since 1993, by taking into account these last physical considerations, a completely new approach to complex systems has been developed [70–74]; the aim was to obtain an approach related to the "natural" behaviour of complex systems based on the "entropy due to irreversibility", usually named entropy generation. Its proof is based on the link [75,76] between Noether's theorem and the Gouy-Stodola one, while the physical hypotheses can be summarized as follows:

a) An open irreversible real linear or non-linear system is considered;
b) Each process has a finite lifetime τ;
c) What happens in each instant in the range $[0,\tau]$ is unknown, but what has happened after the time τ is always known;
d) The local equilibrium is required to define the global thermodynamic quantities;
e) The balance equation is a balance of exergy fluxes.

The result is the extremum entropy generation approach [10], which can be considered as a generalized Gouy-Stodola approach. Moreover, it is a variational approach because it involves only:

a) The work lost due to irreversibility;
b) The environment temperature, always considered constant during any process.

This approach is interesting for science and engineering because it allows us to analyze complex systems, partially inaccessible, about which our knowledge is, consequently, only partial. An example of such systems is the biological system [77–79] in relation to its healthy or diseased behaviour, with particular regards to its conversion of energy, usually known as metabolism. In fact, biological systems are able to adapt to the variation of environmental conditions; indeed, cells attain their "optimal" performance by a selection process driven by their environment. The resultant effect is a redistribution of energy and mass flows in their metabolic network, by using regulatory proteins. Alfred Lotka pointed out that biological systems' efficiency can be described by the principles of thermodynamics [80–83] and, in contemporary scientific approach, this idea has been developed in relation to evolution of living organisms, biogeocenoses and ecosystems and, over all, bioenergetics [2,9,61,84–89]. This thermodynamic approach to biological systems consists in the analysis of the biological optimization process realized by Nature. It is no more than the classical and engineering thermodynamic analysis of the steady-state flux distribution [83], which are, in this case, the metabolic flows, so, in the analysis of metabolic networks, consequently to the results of a sufficiently large set of experiments, the entropy production rate of the cells has been suggested to be maximized at the optimized state [84,85]: Enrico Sciubba proved that the basis of this result can be related to a more general approach to complex and adaptive systems, as the living systems are, and it can be obtained starting from the so-called Lotka principle [83].

In this way the extremum entropy generation approach can represent a new approach to biological systems because it allows us to analyze the steady states of the open systems in relation to their

irreversibility and their interaction with their environment. It represents a completely new viewpoint of the biological systems because:

a) Cells are complex and open systems;

b) They need very complex models to be described, but any of them represent a comprehensive and general theory for the study and the analysis of the living systems; indeed, these models are useful to describe specific phenomena without offering a global approach to the whole living system, essential for the complex interaction inside the system itself;

c) Cells can be simplified by using a black box model, which allow us to consider cells as thermodynamic open, but not completely accessible, black boxes;

d) They spontaneously exchange heat and mass with the environment, in particular heat as a result of the inside irreversible processes (biochemical reactions);

e) This wasted heat can be considered as the 'natural communication' between cells and their environment;

f) Normal and cancer cells have different behaviours, consequently they must exchange differently their wasted heat and, consequently, they must have different metabolisms;

g) In applied thermodynamics this wasted heat is just what the Gouy-Stodola theorem allows us to evaluate.

In this paper, a review of this approach is proposed, in order to highlight the fundamental role of the generalized Gouy-Stodola approach to bioenergetics, with particular interest to its consequences in biomedicine. To do so, in Section 2, the physical bases of the approach proposed are summarized, while in Section 3 the approach itself is developed and discussed and in Section 4 the use in bioenergetics and biomedicine engineering thermodynamics are highlighted. Last, it is useful to consider how this approach could open new frontiers in applied and engineering thermodynamics, and more in general, in energy, power and mechanical engineering towards a new standpoint of living systems analysis, with particular regards to nanosystems, biosystems and medicine. The hope is that this approach could become a new effective research topic, a link between engineering thermodynamics and biomedicine, biomedicine engineering thermodynamics.

2. The Generalized Gouy-Stodola Approach: Fundamentals

Entropy was introduced in classical thermodynamics in relation to the equilibrium states and reversible transformations. It is a state function. When an irreversible system is considered [90,91], mathematical inequalities appear, while physicians and engineers need to use equalities, so entropy generation was introduced just to avoid these inequalities. Thus, the second law defines the entropy variation, ΔS, for an irreversible system, as [10,35]:

$$\Delta S = \int \left(\frac{\delta Q}{T} \right)_{rev} = \Delta S_e + S_g \tag{1}$$

where ΔS_e is the entropy variation that could be obtained through a reversible path on which the system exchanges the same fluxes across its boundaries, S_g is the entropy generation, *i.e.*, the entropy variation due to irreversibility, but during any process, only entropy really varies [49], so nothing is really produced or generated [10,47–51,53,70,71,83,92]. Consequently, entropy generation, the

entropy variation due to irreversibility, S_g, is nothing more than a quantity that allows us to measure how far the system is from the state that the system could attain through a reversible path [37]. The analytical definition of entropy generation is defined as [35]:

$$S_g = \int_0^\tau \dot{S}_g \, dt \qquad (2)$$

where τ is the lifetime of the process under consideration, which can be defined as the range of time in which the process occurs [3,10,35]:

$$\dot{S}_g = \frac{dS}{dt} - \sum_{i=1}^n \frac{\dot{Q}_i}{T_i} - \sum_{\text{in}} G_{\text{in}} s_{\text{in}} + \sum_{\text{out}} G_{\text{out}} s_{\text{out}} \qquad (3)$$

where Q is the heat exchanged, T is the temperature of the thermal source, s is the specific entropy and G is the mass flow. Moreover, for any open system, the entropy balance in a local form can be written as [93]:

$$\frac{\partial s}{\partial t} + v\nabla \cdot \left(\frac{\text{J}_q}{T} + \sum_i \rho_i s_i \left(\dot{\text{x}}_i - \dot{\text{x}}_B \right) \right) = \dot{s}$$

$$\dot{s} = v\sigma \qquad (4)$$

where $s = S/m$, is the specific entropy, S is the entropy, σ is the entropy production density, v is the specific volume, J_q is the heat flow, $\dot{\text{x}}_i$ is the relative velocity in relation to the centre of mass reference, and $\dot{\text{x}}_B$ is the centre of mass velocity. Now, we consider that Gibb's relation can be introduced [93]:

$$T\frac{ds}{dt} = \frac{du}{dt} + p\frac{dv}{dt} - \sum_i \mu_i \frac{dc_i}{dt} \qquad (5)$$

where s is the specific entropy, u is the internal specific energy, v is the specific volume, p is the pressure, μ_i are the chemical potentials, c_i is the concentrations, T is the temperature and $d(\cdot)/dt = \partial(\cdot)/\partial t + \dot{\text{x}}_B \nabla(\cdot)$. We consider also the following relations for the specific internal energy [93]:

$$\frac{du}{dt} = \frac{dq}{dt} - p\frac{dv}{dt} - v\Pi : \nabla\dot{\text{x}}_B + v\sum_k \text{J}_k \cdot \text{F}_k$$

$$\frac{dq}{dt} = -v\nabla \cdot \text{J}_q$$

$$\frac{dc_i}{dt} = -\frac{1}{v}\nabla \cdot \text{J}_i + \frac{1}{v}\sum_j v_{ij} J_j \qquad (6)$$

where q is the heat per unit mass, $\Pi = \mathbf{P} - p\,\mathbf{I}$ with $\mathbf{P}$ total pressure tensor, p hydrostatic pressure and $\mathbf{I}$ identity matrix of which the elements are $I_{jk} = \delta_{jk} = 1$ if $j = k$ and 0 in the other cases, $\mathbf{a}:\mathbf{b} = \sum_{ij} a_{ij} b_{ji}$ is the product between two tensors $\mathbf{a}$ and $\mathbf{b}$, $\text{J}_k = \rho_k \left(\dot{\text{x}}_k - \dot{\text{x}}_B \right)$ is the diffusion flows and $\mathbf{F}_k$ are the forces, J_j is the chemical reaction rate of the j-th chemical reaction and v_{ij} are quantities such that if they are divided by the molecular mass of the i-th component they are proportional to the stoichiometric coefficients. In this way, by introducing Equation (6) in Equation (5), considering the chemical affinity $\mathcal{A}_j = \sum_k v_{kj}\mu_j$, and remembering that $d/dt = \partial/\partial t + \dot{\text{x}}_B \nabla$, Equation (4) gives [93]:

$$\dot{s} = -\frac{v}{T^2}\mathbf{J}_q \cdot \nabla T - v\sum_k \mathbf{J}_k \cdot \nabla\left(\frac{\mu_k}{T}\right) - \frac{v}{T}\Pi:\nabla\dot{\mathbf{x}}_B - \frac{v}{T}\sum_j J_j\mathcal{A}_j + \frac{v}{T}\sum_k \mathbf{J}_k \cdot \mathbf{F}_k \tag{7}$$

from which a general form for the entropy generation can be obtained:

$$S_g = \int_V \left(-\int_o^{\tau_1}\frac{v}{T^2}\mathbf{J}_q \cdot \nabla T \mathrm{d}t - \int_o^{\tau_2}v\sum_k \mathbf{J}_k \cdot \nabla\left(\frac{\mu_k}{T}\right)\mathrm{d}t - \int_0^{\tau_3}\frac{v}{T}\Pi:\nabla\dot{\mathbf{x}}_B\mathrm{d}t - \int_0^{\tau_4}\frac{v}{T}\sum_j J_j\mathcal{A}_j + \int_0^{\tau_5}\frac{v}{T}\sum_k \mathbf{J}_k \cdot \mathbf{F}_k \right)\mathrm{d}V =$$
$$= S_{g,\mathrm{tf}} + S_{g,\mathrm{dc}} + S_{g,\mathrm{vg}} + S_{g,\mathrm{cr}} + S_{g,\mathrm{de}} \tag{8}$$

where [93]:

a) $S_{g,\mathrm{tf}}$ is the entropy generation due to the thermal flux driven by temperature difference;
b) $S_{g,\mathrm{dc}}$ is the entropy generation due to the diffusion current driven by chemical potential gradients;
c) $S_{g,\mathrm{vg}}$ is the entropy generation due to the velocity gradient coupled with viscous stress;
d) $S_{g,\mathrm{cr}}$ is the entropy generation due to the chemical reaction rate driven by affinity, always positive [42–44];
e) $S_{g,\mathrm{de}}$ is the entropy generation due to the dissipation due to work by interaction with the environment.

and τ_i, $i \in [1,5]$, are the lifetimes [10] of any process. It must be highlighted that any work related to electric fields inside or on the boundaries of the systems can be expressed by variation of the affinities of the ions involved, so that any work for internal electric fields is taken into account in the term $S_{g,\mathrm{cr}}$.

Now we have obtained a general analytical expression of the entropy generation. In order to use this quantity in the analysis of the complex systems steady states, it is interesting to understand its physical-mathematical behaviour at the stationary states. To do so, a real system is considered. For such system, the theorem of kinetic energy can be written as [37,94–96]:

$$W_{\mathrm{es}} + W_{\mathrm{fe}} + W_{\mathrm{i}} = \Delta E_{\mathrm{k}} \tag{9}$$

where W_{es} is the work done by the environment on the system, *i.e.*, the work done by the external forces to the border of the system, W_{fe} is the work lost due to external irreversibility, E_{k} is the kinetic energy of the system, W_{i} is the internal work, such that [37]:

$$W_{\mathrm{i}} = W_{\mathrm{i}}^{\mathrm{rev}} - W_{\mathrm{fi}} \tag{10}$$

with $W_{\mathrm{i}}^{\mathrm{rev}}$ being the reversible internal work and W_{fi} the work lost due to internal irreversibility. Moreover, the following relation must be taken in account [37,94–96]:

$$W_{\mathrm{se}} = -W_{\mathrm{es}} - W_{\mathrm{fe}} \tag{11}$$

where W_{se} is the work done by the system on the environment, *i.e.*, the work done from the internal forces to the border of the system. Consequently, the following three equivalent formulation of the first principle can be obtained [94–97]:

$$Q - W_{\mathrm{se}} = \Delta U + \Delta E_{\mathrm{k}}$$
$$Q - W_{\mathrm{i}} = \Delta U \tag{12}$$
$$Q - W_{\mathrm{t}} = \Delta H$$

where W_{t} is the technical work, U the internal energy of the system and H the enthalpy.

In relation to these last equations, it must be highlighted that the system cannot use all the energy inflow [98–100]. Therefore, we must take into account the available energy of the system, named exergy, *B*, *i.e.*, the maximum work that could be done by a system. It is related to a reference environment, assumed to be infinite, in equilibrium, and to enclose all other systems. This environment has a well known temperature, pressure and chemical composition [97,100]. Thus, exergy allows us to measure the potential of the system or flow to cause changes [3,5,6,59–69,87,100], because it is a non-equilibrium system in relation to the reference environment. The upper limit for conversion of heat into work, on a transformation path, is the Carnot efficiency $1—T_2/T_1$, where T_1 and T_2 are the higher and lower temperature of the transformation itself [4,35,93–97]. Now, the exergy rate $\dot{B}_W$ for an open irreversible system can be written as [35,97]:

$$\dot{B}_W = -\frac{d}{dt}\left(E + p_0 V - T_0 S\right) + \sum_{i=1}^{n}\left(1 - \frac{T_0}{T_i}\right)\Phi + \sum_{in} G_{in}\left(h - T_0 s\right)_{in} - \sum_{out} G_{out}\left(h - T_0 s\right)_{out} - T_0 \dot{S}_g \quad (13)$$

while for a reversible system [35,97]:

$$\dot{B}_W^{rev} = -\frac{d}{dt}\left(E + p_0 V - T_0 S\right) + \sum_{i=1}^{n}\left(1 - \frac{T_0}{T_i}\right)\Phi + \sum_{in} G_{in}\left(h - T_0 s\right)_{in} - \sum_{out} G_{out}\left(h - T_0 s\right)_{out} \quad (14)$$

where *E* is the energy, *p* is the pressure, *T* is the temperature, *S* is the entropy, Φ is the heat power, *G* is the mass flow, *h* is the specific enthalpy, *s* is the specific entropy, 0 means ambient, $i \in [1,n]$ the *i*-th thermal source, *in* inflow, *out* outflow and S_g is the entropy generation. Introducing the exergy lost for irreversibility and dissipation, B_λ, it follows that [35,97]:

$$B_\lambda = \int_0^\tau \left(\dot{B}_W^{rev} - \dot{B}_W\right) dt = W_\lambda = T_0 S_g \quad (15)$$

This last Equation (15) represents the statement of the Gouy-Stodola theorem [11–14], and the arguments which hold Equations (13) and (14) its proof.

Now, considering Equations (9)–(11), the work lost due to external irreversibility can be written in relation to the Gouy-Stodola theorem as [4,94]:

$$W_{fe} = T_0 S_g \quad (16)$$

where T_0 is the environmental temperature and S_g is the entropy generation. Consequently, always considering Equations (9)–(11), the link between the internal and the external works lost for irreversibility can be easily obtained [73,101–103]:

$$W_{fi} - W_{fe} = W_i^{rev} + W_{es} - \Delta E_k \Rightarrow W_{fi} - T_0 S_g = W_i^{rev} + W_{es} - \Delta E_k \quad (17)$$

But, another expression of the work lost can be written as [5,83]:

$$\begin{cases} W_\lambda = \int_V \left(\int_0^\tau dt\, T v \sigma - \varphi\right) dV = \left(T - T_0\right) S_g \\ W_\lambda = W_{fi} - T_0 S_g \end{cases} \quad (18)$$

where $\sigma = \delta^2 S_g/\mathrm{d}t\mathrm{d}V$ is the entropy production density, φ is the dissipation function, v is the specific volume, τ is the lifetime of the process and V is the control volume of the system, the internal irreversibility can be easily obtained as [5]:

$$W_{\mathrm{fi}} = \int_V \int_0^\tau \mathrm{d}t \, T v \sigma \, \mathrm{d}V = T S_g \tag{19}$$

which is the analytical expression for the work lost due to internal dissipation.

3. The Generalized Gouy-Stodola Approach: The Entropy Generation Extrema Theorem and Its Consequences

In Section 1, we have highlighted that all the results obtained in the analysis of the processes which occur in open systems are based on the common principle of the least time. This principle holds to the optimal paths approach, based on the minimum momentum approach, which is nothing more than a redistribution energy approach. This last approach has been used in a great number of physical models and consequent engineering applications such as, for example, Fick's law, Fourier's law, Navier's law, the Smoluchowsky correction to Fick's law, the Einstein-Smoluchovsky relation, the Ornstein-Uhlenbeck process, the Kossakowski-Lindblad equation, the Bogoliubov-Born-Green-Kirkwood-Yvon hierarchy, *etc.* [104–120].

All these approaches and models can be obtained by a more general approach, based on the entropy generation extrema theorem [10], that will be proven in this Section, as a generalized consequence of the link between the Gouy-Stodola theorem, Noether's theorem and the Maupertuis principle. Indeed, as a consequence of Noether's theorem, the stationary state dynamics develop following closed paths, while during transitions between two thermodynamic states, these paths are open, such that energy is exchanged with the environment (from a quantum point of view energy is a great number of quanta). Under such conditions, quanta flow spontaneously from a high energy density volume to a low energy density one [121–128], as the second law states. Moreover, "the flow of quanta irreversibly directs to diminish the energy density imbalance between the system and its environment" [129], following the path which minimizes the time, in accordance with the least time principle [121–128].

Now, considering the effect of the potential energies variation can be evaluated as [37,94–96]:

$$\sum_{j=1}^N \Delta E_{\mathrm{p}j} = W_{\mathrm{i}} + W_{\mathrm{es}} \tag{20}$$

where $E_{\mathrm{p}j}$, $j = 1,. \ldots N$, are the potential energies, W_{i} the internal work, and W_{es} the work done by the external forces to the border of the system, and considering also that:

$$\delta W_{\mathrm{es}} + \delta W_{\mathrm{fe}} + \delta W_{\mathrm{i}} = \mathrm{d}E_{\mathrm{k}} \tag{21}$$

it is possible to introduce the thermodynamic Lagrangian as [10,49,71,74,123–132]:

$$\mathrm{d}\mathcal{L} = \mathrm{d}E_{\mathrm{k}} - \sum_{j=1}^N \mathrm{d}E_{\mathrm{p}j} = \mathrm{d}E_{\mathrm{k}} - \left(\delta W_{\mathrm{i}} + \delta W_{\mathrm{es}}\right) = \delta W_{\mathrm{fe}} = \delta W_\lambda \Rightarrow \mathcal{L} = W_{\mathrm{f}e} = -T_0 S_g \tag{22}$$

and the related action as [10,49,71,74,123–132]:

$$\mathcal{A} = \int_0^\tau dt \mathcal{L} = -T_0 \int_0^\tau dt S_g \tag{23}$$

where τ is the lifetime of the process. As a consequence of the least action [123–128], it follows that [3,10,47,49,53,70,71,73,74,101–103]:

$$\delta \mathcal{A} \leq 0 \Rightarrow \delta S_g \geq 0 \tag{24}$$

if it is considered from the environment and [101–103]:

$$\delta \mathcal{A} \leq 0 \Rightarrow \delta S_g \leq 0 \tag{25}$$

if it is considered from inside the system, so the entropy generation is maximum if it is evaluated from the environment and minimum if it is evaluated from the inside of the system [3,10,49,70,71,73,101–103].

As a consequence of the least action principle, the entropy generation results always in an extremum at the stationary states. Moreover, the change in energy always causes a transition between two different thermodynamic states, and it always results in a path-dependent processes, so the entropy generation maxima theorem allows us to obtain information on the behaviour of the whole system after the full development of any process [36]—it is a global approach, so these flows of quanta in a process are nothing more than a flow of exergy. Indeed, considering that [35]:

$$\dot{s}_g = \mathbf{J}_U \cdot \nabla\left(\frac{1}{T}\right) + \sum_i \mathbf{J}_{N_i} \cdot \nabla\left(\frac{\mu}{T}\right) \tag{26}$$

where $\mathbf{J}_U$ is the energy flow, T is temperature, μ is the chemical potential, and $\mathbf{J}_{Ni}$ is the molar flow, it follows that:

$$
\begin{aligned}
(T - T_0)\dot{s}_g &= (T - T_0)\left[\mathbf{J}_U \cdot \nabla\left(\frac{1}{T}\right) + \sum_i \mathbf{J}_{N_i} \cdot \nabla\left(\frac{\mu}{T}\right)\right] = \\
&= T\left(1 - \frac{T_0}{T}\right)\mathbf{J}_U \cdot \nabla\left(\frac{1}{T}\right) + T\sum_i\left(1 - \frac{T_0}{T}\right)\mathbf{J}_{N_i} \cdot \nabla\left(\frac{\mu}{T}\right) = \\
&= T\mathbf{J}_B \cdot \nabla\left(\frac{1}{T}\right) + T\dot{s}_g^{ch}
\end{aligned}
\tag{27}
$$

where $\mathbf{J}_B$ is the exergy flow density and $\dot{s}_g^{ch}$ is the chemical component of the entropy generation density rate. This relation, integrated in time and volume, holds:

$$
\left.
\begin{aligned}
W_\lambda &= W_{fi} - W_{fe} = (T - T_0)S_g = \\
&= T\int_0^\tau d\tau \int_V dV\left[\mathbf{J}_B \cdot \nabla\left(\frac{1}{T}\right) + \dot{s}_g^{ch}\right] \\
W_\lambda &= W_{fi} - W_{fe} = W_i^{rev} + W_{es} - \Delta E_k
\end{aligned}
\right\}
\Rightarrow W_i^{rev} + W_{es} - \Delta E_k = T\int_0^\tau d\tau \int_V dV \mathbf{J}_B \cdot \nabla\left(\frac{1}{T}\right) + T S_g^{ch}
\tag{28}
$$

In this relation it is possible to evince that the system reacts to the external forces by exergy flows. Last, starting from this last relation, it has been proven that [83]:

$$S_g \leq T_0 \frac{T_1 - T_0}{T - T_0} W_{\lambda 1} \quad \forall T \neq T_0 \tag{29}$$

where $W_{\lambda 1}$ is the lost work required to maintain the state 1 at the temperature $T_1 \neq T_0$, in agreement with the previous result Equation (24). This results points out that:

  a) the entropy generation has an upper limit for non-equilibrium states;
  b) the entropy generation has a maximum for the stationary states (sign =).

These results are related also to the Carnot's efficiency. Indeed, considering an ideal system which absorbs the heat Q_1 from the thermostat at temperature T_1, it follows:

$$S_{\text{g}} \leq Q_1 \frac{1}{T_1} \tag{30}$$

This relation was highlighted to be the entropy variation required to maintain the process [5], so considering the second thermostat at temperature T_2 of a cycle, the heat not converted into useful work becomes:

$$Q_2 = T_2 S_{\text{g}} = Q_1 \frac{T_2}{T_1} \tag{31}$$

and the maximum work done by a system operating on a Carnot's cycle results:

$$W = Q_1 - T_2 S_{\text{g}} = Q_1 \left(1 - \frac{T_2}{T_1} \right) \tag{32}$$

which is just the well known Carnot efficiency:

$$\eta = \frac{W}{Q_1} = 1 - \frac{T_2}{T_1} \tag{33}$$

Then, these considerations allow us to interpret the entropy generation as an "exergy footprint Δ" in the environment, due to the processes occurring inside the complex system. This exergy footprint can be defined as the exergy difference in a cyclic transformation. Indeed, following Annila and Salthe, by using Noether's theorem, any stationary system can be defined in term of the following integral [129]:

$$2 \int_0^{\tau} E_{\text{k}} \, \mathrm{d}t = nh \quad \text{with} \quad n \geq 1 \tag{34}$$

with n multiples of quanta and h Planck's constant. By using the previous relations:

$$\left(W_{\text{i}}^{\text{rev}} + W_{\text{es}} \right) \tau = n\pi\hbar + T_0 \, \tau \, S_{\text{g}} \tag{35}$$

Now, if we consider an ideal system without dissipations, it follows that:

$$W_{\text{i}}^{\text{rev}} - W_{\text{se}} = \frac{n\pi\hbar}{\tau} \tag{36}$$

and the considered process results completely reversible. For example we can consider an electronic transition in an atom, for which the difference of the energy Δ in a cycle, *i.e.*, the absorption and emission of a photon:

$$\Delta = \left(W_{\text{i}}^{\text{rev}} - W_{\text{se}} \right) + \left(-W_{\text{i}}^{\text{rev}} + W_{\text{se}} \right) - \frac{n\pi\hbar}{\tau} + \frac{n\pi\hbar}{\tau} = 0 \tag{37}$$

but, if we consider an irreversible process, Equation (35) must be considered and it follows that:

$$\Delta = \left(W_i^{\text{rev}} + W_{\text{es}}\right) + \left(-W_i^{\text{rev}} - W_{\text{es}}\right) + T_0\, S_{\text{g}} + T_0\, S_{\text{g}} - \frac{n\pi\hbar}{\tau} + \frac{n\pi\hbar}{\tau} = 2T_0\, S_{\text{g}} \tag{38}$$

and the exergy balance has a footprint Δ for this irreversible process, so the entropy generation represents the reversible breaking of any process and also the process footprint on the environment, due to irreversibility.

4. An Example of This Thermodynamic Standpoint: Biomedicine Engineering Thermodynamics

The previous results can be useful in the study of a particular complex system, like the living cells. Indeed, in order to live, cells need temperature differences in relation to their environments; for example, for *Streptococcus faecalis* it results around 0.4 ℃ cm^{-1} [133]. As a consequence of the experimental results we can state that [133–148]:

  a) This temperature difference depends on the cell lines;
  b) For any cell line, this temperature difference depends on the cells' metabolism.

This temperature difference causes exergy flows. Equation (8) must be evaluated to obtain the entropy generation of cells. The entropy generation, $S_{\text{g,tf}}$, due to the thermal flux driven by temperature difference can be evaluated considering that:

$$\left.\begin{aligned} \dot{q} &= -v\nabla\cdot\mathbf{J}_{\text{q}} \\[2pt] \nabla\cdot\mathbf{J}_{\text{q}} &\approx \frac{J_{\text{q}}}{l} \end{aligned}\right\} \Rightarrow J_{\text{q}} = -\frac{\dot{q}}{v}l \\[4pt] \left.\begin{aligned} \mathbf{J}_{\text{q}}\cdot\nabla T &= J_{\text{q}}\frac{\Delta T}{l} \\[6pt] \dot{q} - \dot{w} &= v\frac{\Delta u^*}{\tau_1} \approx v\frac{u^*}{\tau_1} \\[6pt] \dot{w} &= 0 \end{aligned}\right\} \Rightarrow \mathbf{J}_{\text{q}}\cdot\nabla T = -\frac{1}{v}\dot{q}\,l\,\frac{\Delta T}{l} \tag{39}$$

consequently:

$$\mathbf{J}_{\text{q}}\cdot\nabla T = \frac{1}{v}\dot{q} = \frac{u^*}{v\tau_1} \tag{40}$$

where $\dot{q}$ is the outflow specific heat power, v is the specific volume, ΔT is the temperature difference between the cell and its environment, u^* is the internal energy density, l is a typical length of a cell, evaluated as the mean diameter of a cell, $\mathbf{J}_{\text{q}}$ is the heat flux, τ_1 is the lifetime of this process, u is the cell internal energy density, and $\dot{w}$ is specific power. Then, it follows that:

$$S_{\text{g,tf}} = -\int_V dV \int_o^{\tau_1} \frac{v}{T^2}\mathbf{J}_{\text{q}}\cdot\nabla T\,dt = \frac{u^*}{T^2}\frac{\Delta T}{\tau_1}V\tau_1 \tag{41}$$

T is the mean temperature of the cell, and V is the volume of the cell such that [149]:

$$V = \frac{\delta_1(t)\delta_2^2(t)}{2} \tag{42}$$

where $\delta_1(t)$ and $\delta_2(t)$ are the longer and the shorter axes dimensions of the cell. Consequently, the characteristic length, previously introduced, results:

$$l \approx \left(\frac{\delta_1(t)\delta_2^2(t)}{2} \right)^{1/3} = \left(\frac{6V}{\pi} \right)^{1/3} \tag{43}$$

considering the cell approximated as a sphere. Last, the quantity $V L/\tau_1$ can be evaluated as:

$$V \frac{l}{\tau_1} = \frac{4\pi}{3} \left(\frac{l}{2} \right)^3 \frac{l}{\tau_1} = \frac{l^3}{6} \frac{\pi l}{\tau_1} = \frac{l^3}{6} \frac{\pi}{\tau_1} \frac{6V}{A} = \frac{l^3}{6} \frac{\pi}{\tau_1} \frac{6V}{Na} = \frac{l^3}{6} \frac{\pi}{\tau_1} \frac{6}{na} \approx \frac{l^3}{6} \dot{x}_{th} \tag{44}$$

where n is the numerical density of the cells, a is the border area of the molecules, and $\dot{x}_{th}$ is the molecular thermal velocity inside the cytoplasm. Therefore, the entropy generation $S_{g,tf}$ due to the thermal flow driven by temperature difference is:

$$S_{g,tf} \approx \frac{u^* l^2 \dot{x}_{th}}{6T^2} \Delta T \tau_1 \tag{45}$$

where τ_1 is the time related to the thermal flow driven by temperature difference, evaluated by considering that the time constant of the thermal transient for heat conduction is [140]:

$$\tau_{cv} \approx \frac{\rho V c}{hA} = \frac{\rho V L c}{0.023 \, \lambda \, A \, Re^{0.8} \, Pr^{0.35}} \tag{46}$$

with $\rho \approx 1000$ kg m^{-3} density, V is cell volume, A is external cell surface, $c \approx 4186$ J kg^{-1}K^{-1} specific heath, h is convection heat transfer coefficient, $\lambda \approx 0.6$ W m^{-1} K^{-1} heat conductibility, L is characteristic dimension of the cell, $Re \approx 0.2$ [150] the Reynolds number and $Pr \approx 7$ [150] the Prandtl number. The process would be occurred in a time $\tau_1 \approx 5\tau_{cv}$, as usually accepted in any physical transient phenomenon [148]. For human cells this value can be considered in the range $15 \div 269$ ms, being the cell volume in the human body in the range 200–15,000 μm^3.

The entropy generation $S_{g,dc}$ due to the diffusion current driven by chemical potential gradients can be evaluated considering that the chemical potential gradient occurs inside the cytoplasm, between the two membrane surfaces. It follows that it can be calculated as $(\mu_{i,os} - \mu_{i,is})/d_m$, where d_m is the depth of the membrane, μ_i is the chemical potential of the i-th species, ρ_i is the concentration of the i-th species, and os and is means respectively *outside* and *inside* the cell, and the diffusion flows $J_i = \rho_i(\dot{x}_i - \dot{x}_B)$ has been calculated as $|\dot{x}_i - \dot{x}_B| \approx \dot{x}_{th}$ and $J_i = \rho_i \dot{x}_{th}$, where $\dot{x}_B$ is the velocity of the centre of mass of the cell, and $\dot{x}_{th} \approx 5 \times 10^{-5}$ m s^{-1} is the relative molecular velocity, inside the cytoplasm. It has been obtained:

$$S_{g,dc} = \int_V dV \int_0^{\tau_2} v \sum_k J_k \cdot \nabla \left(\frac{\mu_k}{T} \right) dt \approx \frac{\dot{x}_{th} V_m}{T} \frac{\sum_i \rho_i \left(\mu_{i,os} - \mu_{i,is} \right)}{d_m} \tau_2 \tag{47}$$

where V_m the membrane volume, and τ_2 is the time related to the diffusion current driven by chemical potential gradients, evaluated as [140]:

$$\tau_2 \approx \frac{d}{D} \tag{48}$$

where $d_m = 0.01$ µm is the length of the membrane and D is the diffusion coefficient. To evaluate this relation, it has been considered the diffusion coefficient of the glucose, which is about 10^{-9} m^2 s^{-1}; it follows that $\tau_2 \approx 10$ s.

The entropy generation $S_{g,vg}$ due to the velocity gradient coupled with viscous stress, has been evaluated considering that the stress tensor $\mathbf{\Pi}$ appears as a consequence of the membrane reaction to the resultant of the external forces acting on the membrane surface itself. But, it is just the energy density due to a viscous tension per unit specific volume $\mathbf{f}_v \sim \eta \nabla \dot{\mathbf{x}}_B^{memb} / v$, where $\eta \approx 6.91 \times 10^{-3}$ N s m^{-2} is the average viscosity coefficient, $\dot{x}_B = |\dot{\mathbf{x}}_B| \approx 3.0 \times 10^{-6}$ m s^{-1} is the velocity of the centre of mass of all components in cell, $\nabla \dot{\mathbf{x}}_B \approx \dot{\mathbf{x}}_B / r$ is its gradient, where $r \approx (3V/4\pi)^{1/3}$ is the mean cell radius, considering an equivalent cell of spherical shape, while $\nabla \dot{\mathbf{x}}_B^{memb} \approx \dot{\mathbf{x}}_B^{memb} / d_e$ is its gradient in relation to the membrane depth, while $d_e = 0.2r$ is the cytoplasm layer. Consequently, this entropy generation component results:

$$
\left.
\begin{aligned}
S_{g,vg} &\approx -\frac{v}{T}\Pi : \nabla \dot{\mathbf{x}}_B \\
\Pi &\approx \frac{\eta}{v}\nabla \dot{\mathbf{x}}_B^{memb}\frac{A}{V} \approx -\eta A \frac{\dot{\mathbf{x}}_B}{Vvd_e} \\
\nabla \dot{\mathbf{x}}_B &\approx \frac{\dot{\mathbf{x}}_B}{r}
\end{aligned}
\right\}
\Rightarrow S_{g,vg} = -\int_V dV \int_0^{\tau_3}\frac{v}{T}\Pi : \nabla \dot{\mathbf{x}}_B\, dt \approx \frac{4\pi\left(\frac{l}{2}\right)^2}{T}\eta\frac{\dot{x}_B^2}{rd_e}\tau_3 \approx \frac{\pi l^2}{T}\eta\frac{\dot{x}_B^2}{\frac{l}{2}0.2\frac{l}{2}}\tau_3 = \frac{20\pi}{T}\eta \dot{x}_B^2\tau_3
\tag{49}
$$

where A is the membrane external surface ($\approx 4\pi l^2$) τ_3 is the lifetime of this process, evaluated by considering the proper propagating time of a mechanical wave on the surface of the cell:

$$
\tau_3 = \frac{2\pi r}{c}
\tag{50}
$$

with $c \sim 1540$ m s^{-1} [140] the sound velocity is considered the same in biological tissue.

The entropy generation $S_{g,cr}$ due to the chemical reaction rate driven by affinity can be evaluated considering the number N_i per unit time and volume of the *i*-th chemical reaction and the chemical affinity $\mathcal{A}$ such that it follows:

$$
S_{g,cr} = \int_V dV \int_0^{\tau_4}\frac{v}{T}\sum_j J_j\mathcal{A}_j \approx V\tau_4 \sum_i N_i\frac{\mathcal{A}_i}{T}
\tag{51}
$$

where τ_4 is the lifetime of this process, evaluated by considering that the magnitude order of a chemical reaction in a cell ($\sim 10^{-7}$ mol s^{-1} L^{-1}) and the moles number are proportional to density of the chemical species (for glucose 1540 kg m^{-3}) and the volume of the cell itself. It follows that this time is in the range $17 \div 1283$ ns. Here some considerations must be added. Moreover, all kinds of ATPases (A-ATPase of Archaea, the E-, F-P- and the V-ATPases) are enzymatic complexes, which work as molecular rotary motors which supply energy to the membrane. Consequently, they generate electrochemical ion gradients across the membrane and hydrolyse or synthesize ATP [141], so, the entropy generation due to the membrane electric potential is considered in this term of the entropy generation.

The entropy generation $S_{g,de}$ due to work dissipated by interaction with the environment is related only to the force generated by the interaction with the external field $\mathbf{F}$ and on the associated flow $\mathbf{J}$:

$$S_{\text{g,de}} = \int_V dV \int_0^{\tau_5} \frac{v}{T} \sum_k \mathbf{J}_k \cdot \mathbf{F}_k \tag{52}$$

where τ_5 is the lifetime of this process. It depends on the interaction under consideration and it is not possible to show a general relation, so Equation (8) for a cell gives:

$$S_{\text{g}} \approx \frac{u^* l^2 \dot{x}_{\text{th}}}{6T^2} \Delta T \tau_1 + \frac{\dot{x}_{\text{th}} V_{\text{m}}}{T} \frac{\sum_i \rho_i \left(\mu_{i,\text{os}} - \mu_{i,\text{is}} \right)}{d_{\text{m}}} \tau_2 + \frac{20\pi}{T} \eta \dot{x}_{\text{B}}^2 \tau_3 + V \tau_4 \sum_i N_i \frac{\mathcal{A}_i}{T} - \int_V dV \int_0^{\tau_5} \frac{v}{T} \sum_k \mathbf{J}_k \cdot \mathbf{F}_k \tag{53}$$

where [137–140] the mean cell temperature can be assumed as $T = 310$ K; the internal energy density can be evaluated as the ratio between the cell mean internal energy, considered the same of the ATP, $U = 3 \times 10^{-7}$ J and the mean value of the cell inside the human body $V = 7600$ μm^3, so it can be considered as $u^* = 3.95 \times 10^7$ J m^{-3}; the thermal molecular mean velocity inside the cytoplasm is considered; the membrane volume is evaluated as:

$$V_{\text{m}} = \frac{4}{3}\pi r^3 - \frac{4}{3}\pi(r - d_{\text{e}})^3 = \frac{4}{3}\pi r^3 - \frac{4}{3}\pi(r - 0.2r)^3 = \frac{4}{3}(1 - 0.2^3)\pi r^3 = \frac{4}{3}0.992\pi r^3 = 0.992V \tag{54}$$

the chemical potential gradient can be evaluated as the ratio between the mean value of the chemical potential $\mu = 1.20 \times 10^{-9}$ J kg^{-1}, being the mean density $\rho = 1000$ kg m^{-3}. So, we can obtain:

$$S_{\text{g}} \approx \alpha \cdot \Delta T \cdot l^2 + (\beta - \kappa)l^3 + \frac{\gamma}{l^2} + \varepsilon l \tag{55}$$

with $\alpha = 3.3 \times 10^{12} \tau_1 / T$, $\beta = 3 \times 10^7 \tau_2 / T$, $\gamma = 4.7 \times 10^{12} \tau_3 / T$, $\varepsilon = 0.523 \tau_4 \sum_i N_i \mathcal{A}_i / T$, and $\kappa = (\pi v \tau_5 / 6T) \sum_k \mathbf{J}_k \cdot \mathbf{F}_k$ constants at defined environmental parameters for any cell line [140]. By using the maximum entropy generation theorem, it is possible to obtain, in term of mass growing [140]:

$$\Delta M = \frac{\zeta' d_{\text{f}} l^{d_{\text{f}}}}{2} \ln\left(\frac{2\gamma - \varepsilon l^3 - 2\alpha l^4 \Delta T - 3(\beta - \kappa)l^5}{2\gamma - \varepsilon l^3 - 2\alpha l^4 \Delta T_0 - 3(\beta - \kappa)l^5} \right) =$$

$$= \frac{\zeta' d_{\text{f}} l^{d_{\text{f}}}}{2} \ln\left[\frac{2\gamma - \varepsilon l^3 - 2\alpha l^4 \left[\frac{l_0^2}{l^2} \Delta T_0 + \frac{2\gamma}{3\alpha}\left(\frac{1}{l_0^2 l^2} - \frac{1}{l^4}\right) - \frac{\varepsilon}{\alpha}\left(\frac{1}{l} - \frac{l_0}{l^2}\right) - \frac{\beta - \kappa}{\alpha}\left(l - \frac{l_0^3}{l^2}\right) \right] - 3(\beta - \kappa)l^5}{2\gamma - \varepsilon l^3 - 2\alpha l^4 \Delta T_0 - 3(\beta - \kappa)l^5} \right] \tag{56}$$

Its shape is represented in Figure 1 for a cancer growth without the effect of any external field, which means $\kappa = 0$. This result completely agrees with the *S*-shape for a tumour growing according to the Gompertz law [151]. It represents a very interesting result because it allows us to highlight the goodness of the thermodynamic theory proposed. Moreover, it follows that the effect of external fields can be obtained only if:

$$\kappa \geq \beta \tag{57}$$

because under this condition the sign of the coefficient $\beta - \kappa$ can change and, consequently, the cancer mass growth changes its behaviour.

Figure 1. The mass variation rate *vs.* diameter variation for a solid cancer under normal conditions, evaluated using the relation Equation (55) with κ = 0.
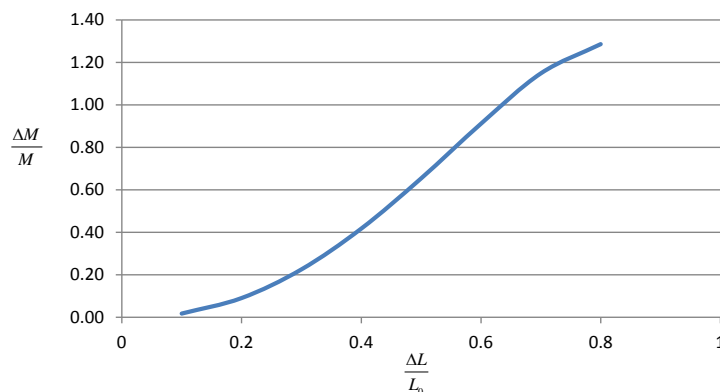
Many experiments support these results, for example, *in vitro*:

a) Human cervical cancer and rat pheochromocytoma cells show a 18.4% and 12.9% decrease, respectively, in cell proliferation when exposed continuously for 72 h to amagnetic field of 1.2 ±0.1 mT, at 60 Hz [142];
b) Human cervical cancer cell proliferation decreased by 15% 24 h after being exposed to a magnetic field of 0.18 T, at 0.8 Hz, for 16 h [143];
c) Human colon adenocarcinoma cells decrease their growth when exposed to 1 Hz for 6 h [144];

and, *in vivo*:

a) Exposure of nude mice bearing a subcutaneous human colon adenocarcinoma (WiDr), to 5.5 mT static magnetic fields for 70 min of exposure a day resulted in a significant increase of survival time, a significant inhibition of tumour growth, a reduction of cell proliferation and an increase of apoptosis in tumours of treated animals [145];
b) Male Fischer-344 rats, subjected to the modified resistant hepatocyte model exposed to 4.5 mT at 120 Hz electromagnetic and magnetic fields showed inhibition of preneoplastic lesions [146].

Many experiments have been developed to obtain the nanomechanical properties of cell membranes, and this approach has been verified by considering just one of them, the experimental results of Pelling *et al*. [147] on the elastic response of the *Saccharomyces cerevisiae* membrane to an external applied force. To do so, we have evaluated [139] the power lost due to the irreversibility for elastic deformation as:

$$\dot{W}_\lambda = \frac{TS_{g,vg}}{\tau_3} \cdot \frac{\Delta V}{V} \tag{58}$$

where ΔV is the variation of the volume due to elastic deformation and the original volume and V is the original volume, so the greater the cell is the less will be the effect of nanomechanical stress. Consequently, the cell membrane changes its behaviour in relation to the mass and electric flows across itself with effects on the chemical reactions inside the cell, but, the elastic power can also be evaluated as [148]:

$$\dot{W}_{el} = \frac{1}{2}\rho A^2 (2\pi v)^2 c \tag{59}$$

where $A = (3.0 \pm 0.5)$ nm is the amplitude of the elastic perturbation, ρ is the density of the medium, $v = 1.6$ kHz is the frequency of the elastic wave and $c \sim 1540$ m s^{-1} is the sound velocity in the medium considered, so, this gives $(1.11 \pm 0.37) \times 10^{-4}$ W. The value obtained by using the $(1.18 \pm 0.04) \times 10^{-4}$ W. These two results agree by 94% and the theoretical value is inside the range of the experimental one.

5. Conclusions

In this paper, the extremum entropy generation approach, a generalized Gouy-Stodola approach, has been developed. The main result of this approach is to be completely independent from the others on entropy and entropy production or generation. Indeed, its hypotheses are completely new, even if, sometimes, it is confused with the other approaches, but as highlighted in Section 1, it is a new standpoint relative to the complex systems and the analysis of irreversibility. Indeed, just the irreversibility is considered the core of the whole approach. The consequence of irreversibility is the work lost, and this is considered as a "natural" communication between the complex system and its environment. This means that, being the complex system partially accessible just due to the irreversible processes, the exergy lost towards the environment can be considered as the information lost on the system, but gained from the environment. Consequently, its analysis plays a fundamental role in the comprehension of the thermodynamic behaviour of complex systems. To develop this analysis entropy generation can be introduced by using the Gouy-Stodola theorem. This allows us to develop a second principle analysis of these kinds of systems.

Last, an example of this approach has been proposed. It is the bioenergetic analysis of a system of cells, in relation to their behaviour as normal or cancerous. The consequence is a completely new viewpoint of cancer, starting from a thermodynamic point of view and linking its analysis to the thermodynamic and biochemical properties of the cell, with particular interest in its metabolism. The results obtained agree with the experimental and theoretical knowledge of cancer, but introduce also new information and a proposal for a thermodynamic electromagnetic anticancer therapy in support to the actual therapies.

This approach can also be compared with other thermodynamic analysis of living systems [152–155]. Indeed, the approach proposed develops a new standpoint in relation to these fundamental previous results. Indeed, our approach suggests how to introduce the lifetime of any process and the way to calculate it. It is fundamental to evaluate the useful quantities (intensity of the field and frequency) for the use of the electromagnetic fields in the suggested anticancer therapy. Our model introduces also the idea that the energy lost by the system is the information gained by the environment, suggesting a new approach to communication between observer and system.

It is opinion of the author that any approach to the system is useful to obtain information on the system itself, and any approach allows us to obtain different information, useful to study new and complementary anticancer therapy.

Conflicts of Interest

The author declares no conflict of interest.

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