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Thermal resonance in living cells to control their heat exchange: Possible applications in cancer treatment

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Abstract

In the end of the second decade of 20th century, Warburg showed how cancer cells present a fermentative respiration process, related to a metabolic injury. Here, an analysis of the cell process is developed, based on its heat outflow, in order to control cancer progression. Engineering thermodynamics represents a powerful approach to develop this analysis. Indeed, the Engineering thermodynamic methods are introduced to analyse the bio-systems, in relation to heat outflow, in order to control this flux. Cells regulate their metabolisms by energy and ion flows, and the heat flux is controlled by the convective interaction with their environment. The bio-thermodynamic characteristic frequency is introduced and it is evaluated by a classical heat transfer approach. Resonance forces natural behaviours of systems, and, here, it is introduced to control both the fluxes, through the cancer membrane, and the cellular metabolic processes. Consequently, the energy available to cancer, for its growth, is controlled, too. The result, experimentally proven, consists in the decrease of rate of cancer growth.

Keywords: Heat transfer in living cells, Cancer, Irreversibility, ELF, Thermal resonance, Entropy.

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1. Introduction

Complex systems are non-linear dynamical systems, composed by interacting subsystems, able to adapt to external perturbations from their environment [1]. Since 1960s, physics and chemistry of complex systems arose as evolving interdisciplinary sciences, and improvements to the dynamical systems theory [2]. Physics and chemistry of complex systems allow us to obtain a mathematical-physical model of many phenomena, such as self-replicating structures, non-equilibrium pattern formation, fluid dynamics, but also cancer growth [3, 4].

In biological and medical sciences, evolution is treated as a strategy of life at the level of organisms [5]. Its basis is an interplay of genetic variation and phenotypic selection [6]. Indeed, genes, and their variants, are selected in relation to their ability of encoding functions, useful to organism survival [7]. This last consideration is particularly true for cancer; indeed, cancer has been modelled as an adaptive system, based on natural selection, in order to allow any single cancer cell to become independent of its neighbours [8]. Indications of its complex adaptive nature can be pointed out by its properties of heterogeneous clonal expansion, replicative immortality, patterns of longevity, rewired metabolic pathways, altered reactive oxygen species, evasion of death signals, metastatic invasion, etc. [2, 8, 9]. Indeed, the fundamental properties of the complex systems, cancer included, are non-linearity, emergence, self-organization, internal interconnection, etc. [3, 10]. In particular [5]:

- Cells behave as agents: they are a set of active elements which interact in a selective way;
- Cancer cells activate some genes, turned off in normal tissues, in order to improve the characteristics useful to their survival: this mechanism generates rules;
- Only the cells with similar adaptive mutations can survive: the components of the system gather together, in relation to their similar abilities;
- Cancer behaviour is non-linear;

- 30 • Genetic instability allows cancer to fit easily and to expand.

Consequently, a new viewpoint emerges in order to model organisms as highly regulated, complex, dynamic systems with meta-stability state around homeostatic levels [11]. The meta-stability state is the result of fluctuations, amplifications and feedback cycles [11] due to continuous oscillations of living
35 systems between order and chaos, promoting survival. This meta-stability is the net result of continuous oscillations, rhythms, networks, amplifications and feedback cycles [12, 13]. In relation to oscillations, the phenomenon of resonance is well known in physics. Indeed, any system presents a proper oscillation frequency, and it can be forced to enter into vibration, if excited by a wave
40 (mechanical or electromagnetic) at the frequencies close to its resonant one [14].

From a thermodynamic viewpoint, a cell is an open system, able to convert its metabolic energy into mechanical and chemical works. The metabolic energy can be modelled as the heat inflow of a thermodynamic system. Consequently, cells can be modelled as thermodynamic engines, which convert part of the
45 inflow heat into work [15]. In this context, normal and cancer cells present two different cellular metabolisms [16]:

- The Krebs cycle: a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl-CoA, derived from carbohydrates, fats, and proteins;
- 50 • The Warburg cycle: a form of modified cellular metabolism found in cancer cells, which tends to favour a specialised fermentation over the aerobic respiration pathway, that most other cells of the body prefer.

In 1931, the Nobel laureate Otto Warburg showed that cancer cells, if compared with the normal ones, follow a different respiration pathway, which is
55 characterized by a glucose fermentation, even when there is no lack of oxygen: this result highlights how the variation on their metabolism is caused by a metabolic injury [17, 18, 19, 20]. Furthermore, the cytoplasmatic cells pH, and the extracellular environment, are directly linked to the cells membrane

potential [21]. Differentiated cells result hyperpolarized in relation to quiescent
60 cells, as Becchetti has shown in Ref. [22].

Any cell, as a thermodynamic engine, must outflow heat into its environment
[15, 23, 24], so, two different cycles are expected to present two different heat
outflows, through the cell membrane. In order to model this process, an equiv-
alent electric circuit of the cell membrane can be considered. But, in electric
65 circuits, both transient and resonant phenomena can occur. So, we consider the
possible equivalent behaviour in the heat transfer, from the cell to its environ-
ment.

In this context, the entropy generation minimization finite time thermo-
dynamics, or thermodynamic optimization, can be considered as a engineer-
70 ing thermodynamic approach to cell systems, because this theory develops the
analysis of optimization of real irreversible systems and processes, subject to
finite-size and finite-time constraints, as deeply developed by Bejan in Ref. [25].
Moreover, the approach, here developed, will consider the fluxes as fundamental
physical quantities in the thermodynamic analysis, following the Bejan's Con-
75 structural law [26] approach, which allows us to consider both the geometrical
properties and the time of exchange of the heat flows, as developed by Bejan
and Lorente in Ref. [27]. Indeed, in living systems, it is a very interesting
approach the analysis of the exchange of entropy, caused by the heat fluxes,
because it plays a fundamental role in the understanding of irreversible chem-
80 ical reactions, as pointed out by Zivieri *et al.* [28]. In this approach, lactic
fermentation and respiration are important metabolic pathways, because life is
based just on them [29]. So, Warburg results will be a starting point for the
thermodynamic considerations, from which the heat and mass transfer, during
glucose catabolism in living systems, and their relation with entropy produc-
85 tion, represent a challenging subject of the classical thermodynamics applied to
biology, as deeply developed Zivieri *et al.* in Ref. [30].

In this paper, the resonant heat transfer, through the cancer cell membrane,
and the influence of low frequencies electromagnetic waves are analysed, in order
to improve the comprehension of the thermodynamic processes which force the

90 decrease of the cancer growth.

2. Materials and Methods

Warburg has shown the metabolic injury in cancer. He pointed out the important role played by the energy conversion in biosystems [17]: cellular biochemical reactions convert external metabolites into cell activities (cell repli-
95 cation, protein synthesis, DNA and RNA transcription and translation, etc.), and wasted heat outflow into cell environment [15, 23]. From a thermodynamic viewpoint, the cell metabolism can be considered as the inflow of energy heat for a direct thermodynamic cycle of a thermal engine, which converts it into thermodynamic useful work and wasted heat.

100 Cells exchange energy and matter through their membrane [31], driven by the endogenous electric fields [32]. The living cell membrane is a double lipid layer that separates the cytoplasm from the external environment. In membranes, some proteins perform a function of channels, across which the inflows and outflows of mass and ions can occur.

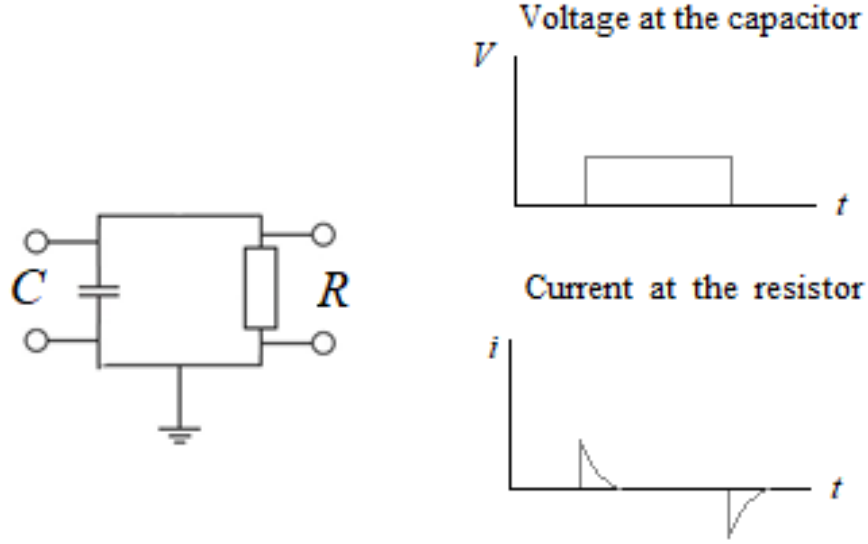
The cell membrane can be modelled as an electric RC circuit (Figure 1) [33]. This kind of circuit presents both transient and resonant behaviour, related to step or harmonic input signals, applied [34, 35]. Now, considering the RC circuit, the transient behaviour of this circuit can be obtained in relation to the current that flows across the resistor of resistance R , during the charge and the discharge of the capacitor [34, 35]:

$$i(t) = \frac{V_0}{R} e^{-t/\tau_{el}} \quad (1)$$

where $i(t)$ is the current, V_0 is the value of electric potential applied to the capacitor, R is the value of the electric resistance, and $\tau_{el} = RC$ is the characteristic time of the system. But, this characteristic time, related to the transient electric phenomenon, is also related to the resonant frequency, which results [34, 35]

$$\nu_{el} = \frac{1}{2\pi \tau_{el}} \quad (2)$$

Figure 1: Electric analogy of a cell membrane. The cell membrane can be considered as a parallel RC circuit [33].



On the other hand, considering the membrane heat transfer, the thermo-kinetic lumped model can be introduced. The cell exchanges heat power with its environment. We stress that this heat outflow is related to the cell metabolism. This heat exchange occurs by convection with the fluids around any cell, and it results in [36]:

$$\dot{Q} = \rho_{cell} V c_{cell} \frac{dT_{cell}}{dt} = \alpha A (T_{cell} - T_{env}) \quad (3)$$

where \dot{Q} is the heat power exchanged by convection, ρ_{cell} is the cell mass density, V is the volume of the cell, c_{cell} is the specific heat of the cell, T_{cell} is the cell temperature, α is the coefficient of convection, A is the surface area of the cell, which varies during the phases of the development of the cell itself, and $T_{cell} - T_{env}$ is the temperature difference between the cell temperature and the environment temperature. As usually done in heat transfer, it is possible to obtain the characteristic time τ_{th} for the thermal transient as [37]:

$$\tau_{th} = \frac{\rho_{cell} c_{cell} V}{\alpha A} \quad (4)$$

105 In analogy with the circuit model of the cell membrane, a resonant effect is expected with a frequency $\nu_{th} \approx 1/\tau_{th}$, under the hypothesis that $\nu_{el} = \nu_{th}$, because the electric circuit is just the theoretical reference model of the cell membrane itself.

Moreover, the heat outflow is the heat wasted by the cell into its environment, as wasted heat consequent to the cell energy cycle. Consequently, the heat exchange process can be modelled as the heat equation for a convective system [37]:

$$\begin{cases} \frac{\partial^2 T}{\partial r^2} - \frac{\Delta H}{\lambda} = \frac{1}{a} \frac{\partial T}{\partial t} \\ \frac{\partial T}{\partial t} = -\frac{\vartheta}{\tau_{th}} \end{cases} \quad (5)$$

110 where r is a radial variable, considering the cell as a theoretical sphere, T is the temperature, ΔH is the metabolism, $a = \lambda/\rho c$, with ρ density and c specific heat, $\vartheta = T - T_0$, with T_0 environmental temperature, $\tau_{th} = \rho c V/(\alpha A)$, with V volume and A area of the cell, and α is the coefficient of convection.

So, if the cancer is irradiated by using an electromagnetic wave, at the resonance frequency ν_{th} , the heat outflow is expected to be forced from the cancer cell to its environment. Consequently, the heat power outflow of the equivalent electric circuit results in:

$$\dot{Q} = RI_M^2 \sin^2(2\pi \nu_{th} t) \quad (6)$$

where I_M is the maximum value of electric current in the equivalent circuit, and \dot{Q} is the time dependent power generated by the fluxes across the membrane equivalent circuit. From a thermodynamic point of view, we can use its effective mean value, which, using the electric circuit theory, results in:

$$\dot{Q} = \int_0^{\tau_{th}} \dot{Q}(t) dt = \frac{RI_M^2}{2} \quad (7)$$

But, at resonant state, the heat outflow is the maximum value of heat we can obtain. Consequently, cancer decreases the energy availability for biochemical processes, such as differentiation, etc., with its growth. So, the increase of heat outflow makes the cancer cell less hyperpolarized, as it can be shown by

considering the Nernst equation, for the cell membrane [15]:

$$\Delta\phi = \Delta G - 2.3 \frac{R_u T_{env}}{F} \Delta\text{pH} = \Delta H - \dot{Q} \tau_{th} - 2.3 \frac{R_u T_{env}}{F} \Delta\text{pH} \quad (8)$$

where ϕ is the cell membrane electric potential, H is the enthalpy, R_u is the universal constant of gasses, F is the Faraday constant, and pH is the potential of hydrogen, and we have considered that the heat power outflow results $\dot{Q} = T_{env}\Sigma$, where Σ is the entropy production rate in the environment and the heat results $Q = \dot{Q}\tau_{th}$. The Equation (8) points out the mechanism of the Extremely Low Frequency Electro-Magnetic Field (ELF-EMF). Indeed, this equation links the quantity $\Delta\phi + 2.3R_uT_{env}\Delta\text{pH}/F$ to the characteristic time, τ_{th} . So, it follows that the membrane electric potential variation $\Delta\phi$ and the pH variation are caused by the characteristic time, at a definite values of inflow energy, ΔH and outflow heat power, \dot{Q} .

In order to prove and confirm this thermodynamic theoretical result, some experiments have been carried out. All of them have always confirmed the theoretical results.

3. Results

Following the second law of thermodynamics, all the biochemical processes require energy. Moreover, any energy conversion process generates outflows of energy. Thus, the cell system behaviour can be analysed, by following an engineering thermodynamic approach, based on the energy and mass balances. In cancer cells, an alteration of some processes, related to energy and ion channelling, has been shown, reducing their proliferation control. Heat transfer through cell membrane can be described by a thermo-kinetic lumped biophysical model. So, we can analyse the cell system as a black box, which is the usual approach used in engineering thermodynamics, considering all the internal biochemical reactions of the cell as the causes of the wasted heat outflows. The variation of the fundamental physical quantities, which control the biochemical reactions, can be controlled by managing the heat transfer. Indeed, an electromagnetic wave, at the thermal resonant frequency, can force the heat transfer

140 with a related change in the membrane electric potential and in pH. The result is
the conditioning of the biochemical reactions and to force these thermo-physical
quantities towards a normal behaviour.

The experimental proofs of these theoretical results have been carried out by
comparing the growth of some cancer cell lines, under the exposure of an ELF-
145 EMF, at their proper characteristic resonant frequencies, with the same lines of
untreated cells. The characteristic resonant frequency has been evaluated for
each cell line, by considering the cells average geometric parameters as required
by the theoretical result, Equation (4). The ELF-EMF exposure system is
constituted by two independent couples of coaxial coils, wound into a cylindric
150 frame (external radius 8 cm, distance between the couple of coils 8 cm). The
outer casing of the exposure system is constituted by a box that shields it from
the background magnetic field, in order to expose the cells at their resonant
frequencies. The treated cells plate was set in the centre of the shielded exposure
system, inside an incubator, while the untreated cells (the control ones) of the
155 same cell line, were placed inside the incubator, without any shield. Some
results obtained are summarised in Table 1, where the resonant frequency has
been calculated for each cancer cell line. The cells have been exposed to their
proper characteristic resonant frequency, and the effect on their growth has been
compared with that of the untreated cells. It is possible to point out that:

- 160 • The electromagnetic waves, at thermal cell resonant frequency, reduce the
growth rate of the cancer;
- The phenomenon is selective in relation to the frequencies used, as it must
be for a resonant process.

Always in Table 1, it is possible to highlight that the cancer growth reduction
165 depends on the frequency, which is a function of the cell lines shapes. It is
possible to suggest that the shape is function of the cell cycle phase. In order
to consider possible applications in therapies, an improvement of the ELF-EM
effect could be obtained by evaluating the mean of the volume/area ratio in
different times of the cell phase.

Table 1: Growth variation of some cancer cell lines after the exposure to the calculated resonant frequencies [38, 39]. In particular, A375P is a human melanoma cell line, HT29 is a human colorectal adenocarcinoma cell line, GTL16 is a human gastric cancer cell line, MCF7, MDA-MB-231 and SKBR3 are three different cell lines of human breast cancer.

Cell line	Frequency [Hz]	Growth variation [%]
A375P	31	-15
HT-29	24	-19
GTL16	14	-24
MCF7	5	-22
SKBR3	8	-18
MDA-MB-231	6	-18

170 **4. Discussion and Conclusions**

The temperature difference, between the inside and outside of any living cell, is fundamental for the cell life, because the related heat flow contributes to entropy variation, with the consequent reorganisation of the cell itself. The heat outflow, and the related entropy production, are caused by the biochemical and biophysical processes inside the cell.

In this paper, the analysis of the thermal resonance of the cell membrane has been developed in relation to the heat exchanged by convection.

The results obtained highlight the fundamental role of the cell volume-area ratio (shape), in relation to the heat fluxes control, with particular regards to the thermal resonant state of living cells.

A characteristic proper time has been pointed out in relation to the response of any cell line to heat exchange, as expected for the resonant phenomena. This time results related to the cell volume-area ratio, a geometrical parameter fundamental for the considerations on fluxes and cells membrane electric potential variation.

Here, previous theoretical results [40, 41, 42] have been improved by focusing the analysis on the equivalent electric circuit model of the membrane. This

is a fundamental result, because it links the previous entropic analysis to the accepted model of membrane, in literature. In this way, the experimental results can be interpreted by linking together the entropic analysis, developed in
190 previous papers, to the electric model of membrane, never considered before this paper in our analyses. The results obtained by these different approaches converge to the same experimental results.

This result represents a new philosophical approach to anticancer therapies, because it is based on biophysical thermodynamics as a new reference for on-
195 cologic methodology. Indeed, the study started from the attempt to treat the cancers that don't respond to the present anticancer therapies, i.e. pancreatic cancer, glioblastoma, lung mesothelioma, etc. So, a possible future therapy could use the ELF-EM in order to decrease the cancer growth, with the consequence of allowing the drugs to obtain desired therapeutic effects. In this way,
200 the ELF-EM approach is considered as a support to the present therapies in order to improve their therapeutic effects, as suggested by experimental evidences in Ref. [39].

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