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RESONANCE IN THERMAL FLUXES THROUGH CANCER MEMBRANE

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(communicated by Paolo V. Giaquinta)

ABSTRACT. Cancer represents one of the most important issues of the biomedical researches, which involve also other sciences, such as mathematics, physics, chemistry, biology, and engineering. In particular, a new thermophysical approach has been suggested and experimentally proved in the analysis of the growth behaviour of cancer cells. In this communication we introduce a theoretical evidence of the resonant behaviour of the heat exchange of the living cell. Last we summarise also the experimental results in support to this theoretical approach.

In this communication we want to analyse the role of heat in the study of the cancer systems, in order to improve the bases of the thermodynamic approach to cancer behaviour in relation to its growth and its interaction with low frequencies electromagnetic waves (ELF). This is useful because, recently, cancer has experimentally been treated by ELF in order to design a possible support to the present anticancer therapies (Lucia *et al.* 2017b). This treatment is the result of a thermodynamic approach, which introduces a new general viewpoint for the analysis of the living systems (Lucia 2013; Lucia *et al.* 2016; Lucia and Grisolia 2017; Lucia *et al.* 2017a; Lucia and Grisolia 2018; Lucia *et al.* 2018, 2019).

Living cells live in an environment which slowly changes its chemical and physical properties. In mammalian animals, organs and tissues are generally endowed with a homeostatic capability, which is characterized by internal thermal regulation. A living system can be defined as an open system, so non-equilibrium thermodynamics, can be applied just to living systems (Miller 1960). Cancer is a living cell with a different growth behaviour in relation to the cell we consider normal. At a definite phase of its life any cancer cell divides into two cells. The size of the single cell at the beginning of division can vary (Koch and Schaechter 1962); consequently, also the relative size of the two daughter cells can vary. In our analysis we consider the lower and upper bounds on cell volume in order to consider the size range of the cell line considered (Errington *et al.* 1965).

The low entropy nutrients which enter into the cells, cancer included, undergo a set of thermochemical processes, which keep the non-equilibrium status of the cell stationary. In thermodynamics the definition of the control volume is fundamental: in this context it could be useful to consider the single cell as the observed control volume, but the usual experimental setup doesn't allow us to introduce such approach, so we are forced to observe

a multitude of single cells and consider this multitude as a system of single cells. Indeed, this approach starts from the consideration of the heat wasted by the cells. In thermodynamics wasted heat is consider as a non-organized information, so we can suppose that this heat isn't an information transfer from a cell to another one. The result is that the wasted heat doesn't represent a communication among cells. Consequently, the effect of our perturbation of the cells can be considered, in first approximation, a perturbation of any single cells, and the total response of all the cells, the sum of the responses of any cell, as the effect on the whole tissue. This system, considered as a single cell in a culture, is an open system from a thermodynamic point of view, so, energy and matter flow through the border of the system, while biochemical and biophysical transformations occur within the system, with a related net production of entropy. The environment of the system considered is composed by the suspending aqueous solution of cell nutrients, the substances discarded by the cells, the gaseous atmosphere above the suspending solution. Consequently, the bio-system is composed of:

- the cell membrane, which delimits the volume of the cell, controls inflows and outflows of molecules;
- the cytoplasm which is an aqueous solution of molecules that fills the cell interior;
- the organelles, suspended in the cytoplasm.

Moreover, the system may contain many substances not initially present in its environment. Many enzymes found in fragments of cytoplasm membranes are often not directly accessible to system environment, while, in the environment, the concentrations of some molecular species decrease in time, and nutrients must flow into the system in order to allow the biochemical reactions to occur and produce macromolecular cell components, with a related increase of the living cell mass and volume (Lamanna and Mallette 1965). These biochemical reactions require energy. This energy is obtained from the same reactions, which involve the nutrients, with a related waste of heat towards the living cell environment. The net effect of all these biochemical reactions is to reduce the entropy of the system, with a related increase of the entropy generation in the environment (Dean and Hinshelwood 1966). The analysis of the chemical species and of their reactions in the living cells have led to some sequences which start with nutrient molecules and end with the formation of living cells substance and waste molecules and waste heat. Too numerous reaction sequences are considered to exist. Moreover, many molecules can be part of more than one sequence, providing coupling of sequences.

From a thermodynamic point of view, life is an organizational process based on biochemical reactions and energy and matter (ions) flows. Just these fluxes of ions induce the biochemical reactions within cells and tissues. Indeed, cells exchange energy and matter through their membrane, in order to maintain their living conditions. All the biophysical and biochemical processes require fluxes of energy, ions and molecules which are controlled by the endogenous electric fields and accumulated in the nm-thin layer of water. In normal cells, mitosis is synchronized with cell growth in order to maintain their size during replication. This biological result represents the bioenergetic basis to link the production of lactic acid and extracellular-intratumoral acidification to cancer growth and metastasis. Moreover, both the pH of the cell cytoplasm and the extracellular environment are controlled by the living cell membrane potential. Differentiated cells are hyperpolarized as compared to quiescent

or cycling cells, and the hyperpolarization increases the efflux of some ions (Ca^{2+}, K^{+}, Zn^{2+}, etc.). Considering the chemical reaction at constant pressure and temperature the Gibbs Free Energy could seem the selected function for the study of the steady states of the living systems, but its decrease as a criterion for occurrence of a spontaneous evolution is limited to the complex phenomena which occur at constant temperature and pressure inside the living system. But, a general objective function for the analysis of the living systems is required.

In normal cells, mitosis is synchronized with cell growth for cells to maintain their size during replication. Even if the tumor behaviour is more complex and it is probably based also on genetic structures of the cells, the results of the Nobel Laureate Warburg highlight the important role of energy conversion in cells (Warburg *et al.* 1927). Indeed, he pointed out the different use of energy in cancer and normal cells. From a thermodynamic point of view, this result allows us to consider the cell as a black box, as usually done in thermodynamics, with a genetic regulation, which disappears in the energy balances. Indeed, the thermodynamic approach evaluates the life cycle of the cell by considering only the energy and mass fluxes balances during the whole cycle of cell life, and not considering the gene activities, but evaluating only their consequences expressed by the energy conversion in cell. Living cells metabolism implies only inflows and outflows of matter and heat through the cell membrane.

In particular, the heat flux is the heat wasted by the cell towards its environment. We can consider that, inside the experimental setup usually used in the biophysical and biochemical analysis of cells, and the general approach to the heat transfer results (Kreith 1973; Nag 2011):

$$\frac{\partial^2 T}{\partial r^2} - \frac{H_M}{\lambda} = \frac{1}{a}\frac{\partial T}{\partial t} \tag{1}$$

$$\frac{\partial T}{\partial t} = -\frac{\vartheta}{\tau} \tag{2}$$

where r is a radial variable, considering the cell as a theoretical sphere, T is the temperature, H_M is the metabolism, $a = \lambda/\rho\, c$, with ρ density and c specific heat, $\vartheta = T - T_0$, with T_0 environmental temperature, $\tau = \rho\, c V/(\alpha A)$, with V volume and A area of the cell, and α is the coefficient of convection. This equation holds to a harmonic solution:

$$T(r) = T_0 + \theta \sin\left(\frac{r}{\sqrt{a\tau}}\right) - \frac{a\tau}{\lambda} H_M \tag{3}$$

Considering the heat exchanged at the cell membrane, this phenomenon occurs by convection with the suspending aqueous solution around any cell, so we can write:

$$\dot{Q} = \rho\, V\, c \frac{dT}{dt} = -\alpha \frac{V}{\langle R \rangle}\left(T - T_0\right) \tag{4}$$

where α is the coefficient of convection, $V/\langle R \rangle$ is the surface area of the cell, which changes with the phases of the development of the cell, V is the volume of the cell, $\langle R \rangle$ is the volume/area ratio, a parameter which influences the chemical reaction time and the fluxes through the cell membrane, ρ is the cell mass density, and c is the specific heat of the cell, and $T - T_0$ is the difference of temperatures between the cell temperature T and the

TABLE 1. Cell parameters and ELF frequencies ν (Hz)

cell line	theory	experiment (Lucia *et al.* 2017b)
MCF7	5.0 ± 0.7	5.0 ± 0.3
SKBR3	8.0 ± 2.0	8.0 ± 0.4
GTL16 [a]	14.0 ± 3.0	14.0 ± 0.7
HT29 [b]	50.0 ± 5.5	50.0 ± 2.5
A375P [c]	31.0 ± 4.6	31.0 ± 1.6
SK-Mel-28 [c]	7.0 ± 1.5	7.0 ± 0.4

[a] gastric cancer cell line
[b] colorectal adenocarcinoma
[c] two different human melanoma cell lines

environment temperature T_0. The term $V/\langle R \rangle$ is the geometric shape of the cell in relation to convection. We must introduce this quantity because at a stage of his life a cell has a definite volume, but it can change its shape in relation to its duplication phase at that time. From this equation it is clear that there exists a proper frequency, ν, of the cell system in relation to heat exchange:

$$\nu = \frac{\alpha}{\rho\, c\, \langle R \rangle} \tag{5}$$

But, what is this frequency? It is difficult to find a response without considering the thermodynamic approach. Indeed, each system presents a proper time of answer to the external thermal perturbation. This frequency is the response of the cell to the external thermal perturbation, the cell heat exchange rate, as it is easy to prove if we consider that:

$$\dot{Q} = Q\,\nu \tag{6}$$

where Q is the heat wasted during the cell life. To prove this statement we evaluate the proper frequency for each cancer cell line and compare the theoretical results with the experimental ones. To do so, we evaluate $\rho \approx 10^3$ kg m^{-3}, $c \approx 4186$ J kg^{-1} K^{-1}, $\alpha \approx 0.023 Re^{0.8} Pr^{0.35} \lambda / \langle R \rangle$, with $\lambda \approx 0.6$ W m^{-1}K^{-1}, $Re \approx 0.2$ the Reynolds number and $Pr \approx 0.7$ the Prandtl number (Lucia 2015a,b). The experimental results confirm the resonant effect, as it is possible to show in Table 1, where in the first column are listed six different human cell lines. In particular the first and the second are two different breast cancer cell lines, GTL16 is a gastric cancer cell line, HT29 is a colorectal adenocarcinoma, A375P and SK-Mel-28 are two different human melanoma cell lines (Lucia *et al.* 2017b).

The results, here obtained, point out the fundamental role of the cell volume-area ratio in relation to the fluxes control. Indeed, there is a temperature difference between the interior of a living cell and its environment. This is a thermodynamic necessity for life. Sensible heat is exchanged between inside and outside of the cell due to this temperature difference. This heat flow contribute to entropy generation in the cell environment and it is fundamental to decrease the entropy within the cell, process required to sustain the cell life. Consideration of the temperature difference between environment and cell interior allows

the introduction of non-equilibrium thermodynamics for the analysis of cells behaviour. Brock suggested that the stability of thermophilic organisms can be attributed to membrane structure properties of these organisms (Brock 1985). The temperature gradient contributes to the flow of substances through the cell membranes of the cell with a consequent influence on metabolic processes (Lucia *et al.* 2015; Lucia and Grisolia 2017, 2018; Lucia *et al.* 2018). The approach here suggested allows us to evaluate the homeostatic cellular response to external perturbations. This response is a thermo-chemical output of the cell in the environment. So, we can suggest that the thermodynamic approach holds to a model of analysis of the action and reaction in terms of membrane flux variation.

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