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A NON-EQUILIBRIUM THERMODYNAMIC APPROACH TO SYMMETRY BREAKING IN CANCER

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ABSTRACT. This paper develops a non-equilibrium thermodynamics approach to oncogenesis, with a particular focus on 'symmetry breaking'. The Onsager phenomenological coefficients are introduced to show the biophysical and thermophysical properties of cellular systems with differences between normal and cancerous cells. Seebeck- and Peltier-like effects are introduced to simplify the description of heat exchange and ion fluxes, in an effort to characterize the distinct role of the cellular electric membrane potential. Our results indicate that oncogenesis leads to changes in: (i) the thermophysical properties of the cell cytoplasm, caused by differences in density and heat capacity, (ii) the interactions with the micro-environment, (iii) geometrical characteristics, both in fractal dimensions and in shape symmetry, and (iv) the constitutive properties of membrane fluxes. This presents a unifying biophysics concept for such diverse characteristics, and it may yield new diagnostic and therapeutic opportunities.

1. Introduction

Cancer continues to be a significant medical challenge. It presents with structure-independent functional abnormalities, particularly as it pertains to metabolism, as well as epigenetic and transcription factor dysfunction (Frost *et al.* 2018). Since 1860, the scientific approach to cancer focuses mainly on its origin, i.e. its structural abnormalities, mutations and translocations, with particular regards to DNA organization (Beale 1860; Pienta *et al.* 1989; Bhagwat and Vakoc 2015).

Recently, complex systems have been understood to share universal design patterns even if they occur in different systems (Schrödinger 1944; Nicolis and Prigogine 1989; Waldrop 1993; Mitchell 2009; Ma'ayan 2017). The science of complex systems theory is continuously growing, with the aim to introduce a new approach to understand natural systems (Ma'ayan 2017). In that context, cancer has also been considered as a complex system, with relation to cancer adaptability to environmental changes, with particular interest to the likes of fluxes (heat, nutrients, oxygen, etc.), pH variations, and temperature dependence. This led to a new viewpoint to study the disease with an emphasis on understanding its causal relationships to discover and develop new and more effective treatments (Weinberg 2014; Frost *et al.* 2018). Indeed, oncogenesis is thought of the transformation of a well-regulated

normal cell to a 'chaotic' cancer cell. A completely new approach to oncogenesis has recently been introduced, studying it as a phase transition, thereby using the same approach of physics to changes in structure, function and information (Davies *et al.* 2011).

In this context, we must recall that symmetry is a type of invariance which allows a mathematical entity to remain unchanged, under a set of transformations (Capobianco 2020). From a physical-mathematical viewpoint, a symmetry is a measurable function which maps a mathematical object onto itself, preserves its structure, and makes it no longer identifiable from the given original mathematical object. The spontaneous approach to avoid this consequence is to reparametrise the model, or to constrain the parameters (Capobianco 2020).

In this line of thought "symmetry breaking" emerges (Frost *et al.* 2018) due to the fundamental role of symmetry in cancer biophysics (Capobianco 2019); indeed, biological signals may generate differences in the balance between symmetric and asymmetric cell division, which triggers the differentiation arrest in cancer growth (Shahriyari and Komarova 2013). Moreover, while asymmetric division is considered important for the biological improvements, its dysregulation can promote oncogenesis. As such, cancer symmetry concepts advanced the understanding of e.g. homeostasis loss in cancer as well as its origin, spread, treatment and resistance (Frost *et al.* 2018).

Along this viewpoint, here, we will develop a non-equilibrium thermodynamic analysis of the cell systems, in relation to the fluxes across the cell membrane, in order to try to understand the differences in symmetry breaking between normal and cancer cells.

2. Materials and methods

The membrane of living cells exhibits differential permeability related to specific ions (Na^+, K^+, Cl^-, Ca^{2+}, etc.), which generate an electric potential difference $\Delta\phi$, between the cytoplasm and the extracellular environment, in relation to the environment itself (Yang and Brackenbury 2013). A cell is defined as 'depolarized' if its electric potential difference is relative less negative compared to the reference value of a normal living cell, or defined as 'hyperpolarized' if it is more negative. Since 1956, it emerged that cancer cells are electrically different from normal cells (Ambrose *et al.* 1956; Cone Jr. 1969, 1970, 1971), but, recently, it has also been pointed out how intercellular communications can modify just the membrane electric potential (Yang and Brackenbury 2013). This membrane potential can be evaluated by using a modified Goldman Hodgkin Katz equation (Goldman 1943; Hodgkin and Katz 1949; Grabe *et al.* 2000; Lucia and Grisolia 2020a):

$$\Delta\phi = \frac{RT}{F}\ln\left(\frac{P_{Na^+}[Na^+]_{outside} + P_{K^+}[K^+]_{outside} + P_{Cl^-}[Cl^-]_{outside}}{P_{Na^+}[Na^+]_{inside} + P_{K^+}[K^]_{inside} + P_{Cl^-}[Cl^-]_{inside}}\right) \tag{1}$$

where [A] is the concentration of the ion A, $R = 8.314$ J mol^{-1}K^{-1} is the universal constant of ideal gasses, T is the absolute temperature, F is the Faraday constant, and P stands for the relative permeability such that $P_{Na^+} = 0.04$, $P_{K^+} = 1$ and $P_{Cl^-} = 0.45$.

Our aim is to introduce a non-equilibrium thermodynamic approach, so, we must use these general phenomenological relations (Callen 1960; Yourgrau *et al.* 1982; Lucia and

Grisolia 2020a,b):

$$\begin{cases} \mathbf{J}_e = -L_{11}\frac{\nabla\phi}{T} - L_{12}\frac{\nabla T}{T^2} \\ \mathbf{J}_Q = -L_{21}\frac{\nabla\phi}{T} - L_{22}\frac{\nabla T}{T^2} \end{cases} \tag{2}$$

where $\mathbf{J}_e$ is the current density [A m^{-2}], $\mathbf{J}_Q$ denotes the heat flux [W m^{-2}], T is the living cell temperature and L_{ij} represent the phenomenological coefficients, such that (Katchalsky and Currant 1965) $L_{12} = L_{21}$ in absence of magnetic fields, and $L_{11} \geq 0$ and $L_{22} \geq 0$, and (Katchalsky and Currant 1965) $L_{11}L_{22} - L_{12}^2 > 0$. The cell's life cycle then consists of (Schrödinger 1944):

- a continuous energy generation (metabolism), due to the ion fluxes;
- a continuous heat flux from the cell to its environment.

We can obtain a thermodynamic approach for the cell cycle by introducing two physical mathematical simplifications into Eq. (2), by separating the two processes, under the assumption of independence of the processes from one another:

- the ions and metabolites fluxes can be described by imposing $\mathbf{J}_e \neq \mathbf{0}$ and $\mathbf{J}_Q = \mathbf{0}$;
- the heat exchange towards the environment can be described by imposing $\mathbf{J}_e = \mathbf{0}$ and $\mathbf{J}_Q \neq \mathbf{0}$.

Consequently, so $\mathbf{J}_Q = \mathbf{0}$, cells exchange metabolites and ions such that (Callen 1960; Yourgrau *et al.* 1982):

$$\frac{dc_i}{dt} = -\nabla \cdot \mathbf{J}_i \tag{3}$$

where c_i depicts the concentration of the i-th ion (Na^+, K^+, Ca^{2+}, Cl^-, etc.), t is the time and $\mathbf{J}_i$ stands for the current density of the i-th ion. If the ion fluxes are continuously null, the cell cannot develop biochemical reactions to sustain the cellular life (Schrödinger 1944; Lucia and Grisolia 2020a); consequently $\mathbf{J}_e \neq \mathbf{0}$, so (Callen 1960; Yourgrau *et al.* 1982):

$$\frac{d\phi}{dT} = -\frac{L_{21}}{L_{11}}\frac{1}{T} \tag{4}$$

which allows us to point out that a Peltier-like effect occurs, with a related membrane electric potential variation which causes a temperature variation. Consequently, a related heat flux is generated (Callen 1960; Yourgrau *et al.* 1982; Lucia and Deisboeck 2018; Lucia *et al.* 2018):

$$\frac{du}{dt} = -\nabla \cdot \mathbf{J}_u \tag{5}$$

Next, the related specific entropy rate can be obtained as follows (Lucia and Grisolia 2017):

$$\int_V T\frac{ds}{dt}dV = \int_V \nabla \cdot \left(\mathbf{J}_u - \sum_{i=1}^{N}\mu_i\mathbf{J}_i\right)dV - \int_V \left(\sum_{i=1}^{N}\mathbf{J}_i \cdot \nabla\mu_i\right)dV \tag{6}$$

where s denotes the specific entropy, T is the temperature and μ is the chemical potential, $\mathbf{J}_S = \mathbf{J}_u - \sum_{i=1}^{N}\mu_i\mathbf{J}_i$ represents the contribution of the inflows and outflows, and $T\sigma = -\sum_{i=1}^{N}\mathbf{J}_i \cdot \nabla\mu_i$ is the dissipation function (Yourgrau *et al.* 1982), and, finally, V describes

the cell volume. We can then state that diffusion is caused by the gradient of the chemical potential:

$$\mu_i = \left(\frac{\partial G}{\partial n_i} \right)_{T,p,n_{k\neq i}} \tag{7}$$

where G is the Gibbs energy, n is the number of moles and p stands for the pressure. Up until now, we have considered a flux in accordance with the concentration gradient. But, in the case of fluxes against the concentration gradients it is possible to introduce (Callen 1960; Yourgrau *et al.* 1982):

$$\mathbf{J}_i = -\sum_{k=1}^{N} L_{ik} \nabla \mu_k \tag{8}$$

together with the Gibbs-Duhem relation (Callen 1960):

$$\nabla \mu_N = \sum_{i=1}^{N-1} \frac{c_i}{c_N} \nabla \mu_i \tag{9}$$

Consequently, the Onsager's reciprocity relations are not satisfied, but, if we consider:

$$\mathscr{L}_{ik} = L_{ik} - \frac{c_i}{c_N} L_{iN} \tag{10}$$

where $\mathscr{L}$ denotes the real measurable quantities, it is possible to obtain (Yourgrau *et al.* 1982):

$$\mathbf{J}_i = -\sum_{k=1}^{N-1} \mathscr{L}_{ik} \nabla \mu_k \tag{11}$$

with $\mathscr{L}_{ik} = \mathscr{L}_{ki}$ and

$$T\sigma = -\sum_{i=1}^{N-1} \mathbf{J}_i \cdot \nabla \mu_i \tag{12}$$

The entropy outflow is fundamental in order to generate order from disorder, as Schrödinger himself pointed out (Schrödinger 1944).

Now, the other case must be considered: when $\mathbf{J}_e = \mathbf{0}$, the membrane potential and the pH can be maintained constant if

$$\begin{cases} \frac{\nabla T}{T} = -\frac{L_{11}}{L_{12}} \nabla \phi \\ \mathbf{J}_Q = \left(L_{22} \frac{L_{11}}{L_{12}} - L_{12} \right) \frac{\nabla \phi}{T} \end{cases} \tag{13}$$

It is possible to highlight a Seebeck-like effect in the cell membrane. Then, we consider that:

$$\dot{Q} = \int_A \mathbf{J}_Q \cdot \hat{\mathbf{n}} \, dA \tag{14}$$

where A is the area of the membrane's external surface. And so, it follows:

$$\delta\dot{Q} = \left(L_{22}\frac{L_{11}}{L_{12}} - L_{12} \right) \frac{\nabla\phi}{T} \cdot \hat{\mathbf{n}}\, dA = \frac{k}{T}\, \nabla\phi \cdot \hat{\mathbf{n}}\, dA \tag{15}$$

where $k = (L_{22}L_{11}/L_{12}) - L_{12}$ is a thermoelectric property of the cell which expresses the relation between the membrane's electric gradient and the heat flux, exchanged by convection (Lucia and Grisolia 2020c):

$$\delta\dot{Q} = \rho\, c\, \frac{dT}{dt}\, dV = -\alpha\, (T - T_0)\, dA \tag{16}$$

where $\rho \approx 10^3$ kg m^{-3} denotes the cell density, $c \approx 4186$ J kg^{-1} K^{-1} is the specific heat of the cell, $\alpha \approx 0.023\, Re^{0.8} Pr^{0.35} \lambda / \langle R \rangle$ is the coefficient of convection, with $\lambda \approx 0.6$ W m^{-1}K^{-1} conductivity, $Re \approx 0.2$ the Reynolds number and $Pr \approx 0.7$ the Prandtl number (Lucia and Grisolia 2020c), A depicts the area of the cell membrane, V is the cell volume, and $\langle R \rangle = dV/dA \approx V/A$ is the mean radius of the cell. It then follows that:

$$\frac{d\phi}{d\ell} = -\frac{\alpha}{\left(L_{22}\frac{L_{11}}{L_{12}} - L_{12} \right)}\, T\, (T - T_0) = -\frac{\alpha}{k}\, T\, (T - T_0) \tag{17}$$

which highlights the relationship between the gradient of the membrane's electric potential and the temperature of the cell, being ℓ the length of the membrane. Furthermore, this relation points also out that cell life can be realised, in normal conditions, only if the cell membrane is hyperpolarized. As a result, the cell life cycle consists of (Schrödinger 1944):

- a continuous metabolic generation, due to ion fluxes, related to a Peltier-like effect: $d\phi/dT = -L_{21}/L_{11}T$
- a continuous heat exchange, towards the environment, related to a Seebeck-like effect: $d\phi/d\ell = -\alpha\, T\, (T - T_0)/k$

Now, we consider that life is a continuous transition from the Peltier-like effect to the Seebeck-like one, and *viceversa*. It means that there exists a particular time in which this transition occurs, so, from the previous relations:

$$\frac{d\phi}{dt} = \frac{\alpha}{\rho c}\, \frac{dA}{dV}\, \frac{L_{12}}{L_{11}}\, (T - T_0) \tag{18}$$

Now, we can consider that the heat flux is the heat lost by the cell towards its environment, so, as recently obtained in (Lucia and Grisolia 2020c; Lucia *et al.* 2020):

$$\begin{cases} \dfrac{\partial^2 T}{\partial r^2} - \dfrac{H_M}{\lambda} = \dfrac{1}{a}\, \dfrac{\partial T}{\partial t} \\ \dfrac{\partial T}{\partial t} = -\dfrac{\vartheta}{\tau} \end{cases} \tag{19}$$

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 being the area of the cell, and α is the coefficient of convection. In relation to the geometric variables, this equation holds to a harmonic solution (Lucia and Grisolia 2020c,d; Lucia *et al.* 2020):

$$T(r) - T_0 = \theta \sin\left(\frac{r}{\sqrt{a\tau}}\right) - \frac{a\tau}{\lambda} H_M \tag{20}$$

Consequently, it follows:

- for the continuous metabolic generation, considering Eq. (20): $d\phi/dr = -(L_{21}/L_{11}T)\, dT(r)/dr$, $r \in [R_{cyt}, R_{cyt} + \ell]$, where $R_{cyt} \approx V/A$ is the radius of the cytoplasm and ℓ stands for the cell membrane depth, so:

$$\Delta\phi = -2 \sin\left(\frac{\ell}{2\sqrt{a\tau}}\right) \frac{L_{21}}{L_{11}} \frac{T - T_0}{T} \cos\left(\frac{V}{A} + \frac{\ell}{2\sqrt{a\tau}}\right) \tag{21}$$

- for the continuous heat exchange, towards the environment, considering Eq. $(19)_2$ it follows:

$$\Delta\phi = \frac{\alpha}{\rho c} \frac{A}{V} \frac{L_{12}}{L_{11}} \left[(T - T_0) \sin\left(\frac{1}{\sqrt{a\tau}} \frac{V}{A}\right) - \frac{a\tau}{\lambda} H_M \right] \tag{22}$$

As such, we note that the membrane electric potential rate depends on:

- the thermophysical properties of the cytoplasm, the density ρ and the specific heat c;
- the interaction with the environment, the convective coefficient α, τ, and a, also due to the velocity of blood and fluids around the cell;
- the geometrical properties of the cell, the shape A/V;
- the Onsager phenomenological coefficients, which express the constitutive properties of the fluxes, through the cell membrane.

So, the fundamental difference in behaviour between cancerous and normal cells, can be explained through the geometrical properties of the cell and in the shape of the cell.

These statements agree with the experimental results presented in the literature. Indeed, it has been found that a tumour has a higher fractal mass dimension in comparison with the normal tissues (Cross 1997; Baish and Jain 2000; Dey and Mohanty 2003; Norton 2005); for example, infiltrating ductal breast adenocarcinomas have a fractal dimension of 2.98, while normal breast tissue has a fractal dimension of 2.25 (Norton 2005). The consequence is that the tumour maintains a high density as it grows, with a related higher growth rate and a larger final size. It has been pointed out that this high fractal dimension is due to the structure of the breast cancer, which can be considered as a conglomerate of many small Gompertzian tumours, each of which has a high cell density and hence (high) ratio of mitosis to apoptosis (Norton 2005).

3. Results

The aim of this paper is to propose a non-equilibrium thermodynamic approach to oncogenesis, with particular focus on symmetry breaking. In this context, the Onsager

phenomenological coefficients have been introduced to highlight the biophysical and thermophysical properties of the cell system. In this way, cancer and non-cancerous, normal cells can be studied with regards to their distinct differences. In particular, the fundamental role of the cell's electric membrane potential has been emphasized with regards to ion and heat fluxes. Indeed, a strict relationship between heat exchange and the membrane's electric potential emerges. Moreover, we point out a continuous transition between two thermoelectric effects:

- the Seebeck-like effect, useful to describe heat exchange;
- the Peltier-like effect, helpful in describing ion fluxes.

Of course, these effects occur at the same time, but for a more effective analysis of the cell system, they can be studied separately. Consequently, we must find a time in which a transition between the two effects occurs, and at that time a rate of change in the membrane electric potential can be evaluated. This change is strictly related to the properties of the cell system, and as such it is useful to point out the differences between normal and cancer cells, for the purposes studied here. In particular, we have suggested that, the membrane's electric potential change depends on:

- the thermophysical properties of the cell cytoplasm;
- the cell's interaction with the environment;
- the geometrical properties of the cell;
- the constitutive properties of the fluxes across cell membranes.

As to distinguishing between cancer and normal cells using a "symmetry breaking" concept rooted in thermodynamics, we found that oncogenesis eventually leads to changes in the:

- thermophysical properties of the cytoplasm, which emphasizes different density and heat capacity;
- interactions with the micro-environment, i.e. cancerous cells communicate differently with the environmental structures, (non-cancerous or cancerous) cells included;
- geometrical characteristics, both in fractal dimensions, in agreement with the results reported in the literature (Cross 1997; Baish and Jain 2000), and in shape symmetry;
- constitutive properties of fluxes, which in turn yields that the electric membrane potential must be different in cancerous vs. non-cancerous, normal cells.

4. Discussion and conclusions

Normal cells and multicellular tissues thrive by controlling symmetry, and breaking it, only when it is necessary for biological functions (Frost *et al.* 2018; Capobianco 2019). On the contrary, carcinogenesis is a complex phenomenon which, amongst many interdependent factors, involves alterations in the DNA, in the resulting proteins and cell structure, and in intra- and intercellular communication (Frost *et al.* 2018; Capobianco 2019). The complexity of cancer is generated by the great number of interactions among any structure and component of the system, across scales: among molecules, with cells in the environment, and with organ systems of the host (Frost *et al.* 2018). As such, from a viewpoint of physicists, cancer can be considered as a many body problem: the great number of interactions generates non-linearity and complexity (Chauviere *et al.* 2010).

We then argue that a fundamental role is played by the thermodynamic quantity of entropy, because it allows us to account for the stochastic behaviour of symmetries, based on network ensembles. Indeed, Eq. (9) points out that, when a flux against the concentration gradient occurs, one chemical potential results as a linear combination of the other chemical potentials: in cancer this effect is amplified and so it seems that a malignant tumour is characterised by a degeneracy in its phase space; it leads to an increasing probability of realisation of its stationary state.

In this paper, we have obtained a description of the biophysical basics for symmetry and symmetry breaking in relation to:

- the properties of the biological material;
- the topological properties of the cells;
- the communication within cell networks;
- the fundamental role of the cell membrane's electrostatic potential.

Cancer cells present a broken symmetry in their shape. This seems to be one of the fundamental keys to pathological diagnosis, therapy and prognosis (Frost 2018). Following Frost (Frost 2018), we highlight that the fundamental question to pursue are:

- the origin of the broken symmetry of a cancer cell at a molecular level;
- the link between the symmetry loss and prognosis;
- the relation between homeostasis breaking and symmetry breaking.

Moreover, in this context, we must point out that the identification of anomalies from cell behaviour and patterns is helpful in identifying symmetry breaking. Still, the control of cancer behaviour can depend on the identification of minor biophysical input. Indeed, the identification of symmetries in a biophysical network may improve our knowledge of its organizational rules, fundamental to understand the principles of dynamic control of the biosystem (Capobianco 2019, 2020).

We therefore propose a thermodynamic concept in which thermoelectric effects can be considered to improve the study of the biophysical and biochemical properties of a cancer system in comparison with the non-cancerous, normal tissue, and claim to use these effects as new target areas for innovative therapeutic approaches. This conjecture is supported by several experimental and clinical findings in the literature. For instance, using differential scanning calorimetry, Sano *et al.* (2019) found differences in heat capacity between normal brain tissue and that of malignant brain tumors, with implications on the commonly used laser interstitial thermotherapy. Such differences also have prognostic relevance for recurrent brain tumors (Tsvetkov *et al.* 2018). Furthermore, the mean membrane potential in breast biopsy tissue from 9 women with infiltrating ductal carcinoma was found to be depolarized, as compared to the tissue from 8 women with benign breast disease (Marino *et al.* 1994). Indeed, depolarization has been noted in transformed breast epithelial cells, which were particularly sensitive to the action of K^+ channel blockers (Marino *et al.* 1994). These results could be of significance relevance for patients with triple-negative breast cancer for which a new therapeutic approach is needed. Specifically, the gene KCNMA1 was found to encode the voltage- and calcium-dependent large-conductance potassium channel, which is overexpressed in triple-negative breast cancer patients. Treatment of this channel causes a hyperpolarization of the membrane potential with a consequent cell cycle arrest in G2 phase and apoptosis via caspase-3 activation, showing a potential new anticancer approach

to this tumour type (Sizemore *et al.* 2020). Moreover, it has also been shown that constant calcium influx can selectively kill human triple-negative breast tumour cells (Yu *et al.* 2017). Furthermore, cancer progression occurs together with alterations in the surrounding stroma due to the ability of cancer to generate modification in its microenvironment, by mass fluxes of various cytokines, chemokines, and other factors. Communication, between cancer cells and the neighbouring immune cells, promotes tumour growth and metastasis (Hinshaw and Shevde 2019). The comprehension of this interaction could represent an improvement for a new approach in anticancer therapy, and our approach moves just in this direction. Lastly, in relation to prevention and diagnosis, the transport differences between normal and tumour tissues - also related to the fractal geometry of the tissues - might represent a promising, future avenue for diagnostic imaging modalities (Baish and Jain 2000).

In summary, following a thermodynamic concept and focusing on symmetry-breaking, we postulate that oncogenesis leads to changes in: (i) the thermophysical properties of the cell cytoplasm, (ii) the interactions with the micro-environment, (iii) the geometrical characteristics, and (iv) the constitutive properties of membrane fluxes. While some if not most of these conjectures, in isolation, are already supported by experimental and clinical evidence, a fundamental, unifying biophysics concept has been missing. We argue that this new conceptual framework has the potential to present innovative diagnostic and therapeutic opportunities.

Authors' contributions

Conceptualization, U.L. and T.S.D.; methodology, U.L., G.G. and T.S.D.; software, G.G.; validation, G.G. and U.L.; formal analysis, U.L. and T.S.D.; investigation, G.G.; resources, U.L. and G.G.; data curation, G.G.; writing–original draft preparation, U.L., G.G. and T.S.D.; writing–review and editing, U.L., G.G. and T.S.D.; visualization, U.L., G.G. and T.S.D.; supervision, T.S.D.; project administration, U.L.; funding acquisition, U.L. and G.G.. All authors have read and agreed to the published version of the manuscript.

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