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A thermodynamic approach to the 'mitosis/apoptosis' ratio in cancer

Umberto Lucia [a,*], Antonio Ponzetto [b], Thomas S. Deisboeck [c,1]

[a] Dipartimento Energia, Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy
[b] Department of Medical Sciences, University of Torino, Corso A.M. Dogliotti 14, 10126 Torino, Italy
[c] Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA

HIGHLIGHTS

- Mitosis/apoptosis ratio are fundamental in cancer analysis.
- Cancer can be studied as an open thermodynamic system.
- Mitosis/apoptosis ratio can be related to the cancer irreversibility.
- Engineering thermodynamics allows us to explain the cancer behavior.

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ABSTRACT

Cancer can be considered as an open, complex, (bio-thermo)dynamic and self-organizing system. Consequently, an entropy generation approach has been employed to analyze its mitosis/apoptosis ratio. Specifically, a novel thermodynamic anticancer strategy is suggested, based on the variation of entropy generation caused by the application of external fields, for example electro-magnetic fields, for therapeutic purposes. Eventually, this innovative approach could support conventional therapies, particularly for inoperable tumors or advanced stages of cancer, when larger tumor burden is diagnosed, and therapeutic options are often limited.

1. Introduction

Recently, a new interdisciplinary approach [1], based on a thermodynamic analysis of the irreversibility of the open real systems, has been introduced to analyze the V-ATPase mechanism and its consequences in the behavior of the cell. An improvement of this approach consists in the analysis of the mitosis/apoptosis processes, which is the object of this paper.Conventionally, cancer is understood as a set of malignant cells, which lost their growth control and which exhibit eventually an invasive and metastatic phenotype through a process called carcinogenesis [2–6]. As a consequence, their number and density increases, and they spread. But, recently, other related properties of cancer systems have been highlighted, i.e.:

1. Precursor cells, often present in cancers, emphasize a relationship between cancer cells and their stroma. In fact, a fundamental interaction between the tumor and its environment has been emphasized [7–11].
2. Neovascular blood vessel formations that nourish cancer growth [3](regardless of the fact that avascular tumor growth conditions have been discovered also [4]).

* Corresponding author.
E-mail addresses: umberto.lucia@polito.it (U. Lucia), antonio.ponzetto@unito.it (A. Ponzetto), deisboec@helix.mgh.harvard.edu, ts.deisboeck@thinkmotu.com (T.S. Deisboeck).
[1] Current address: ThinkMotu LLC, Wellesley, MA 02481, USA.

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Moreover, some other results must be considered [4]:

(i) There are genes that control mitosis and apoptosis, and that are differentially expressed in cancer cells; these genes are expressed also in pre-neoplastic states;
(ii) Some genes related to the cancer's growth potential and to its invasive behavior;
(iii) Cancer has an advantageous mitosis-to-apoptosis turnover ratio in that many more cells are generated through replication while comparatively less cells die [4–6].
(iv) Biopsy samples obtained from macroscopically normal organs may contain foci of partially transformed tissue, quiescent only until they are in contact with fibroblasts, which send out physiological growth signals [3].

As such, cancer emerges through a series of steps thought to be sequential, as a disease of abnormal growth driven by local cellular expansion, adjacent tissue infiltration, and distant metastases. Consequently, one of the fundamental approaches to carcinogenesis consists of investigating the derangement of mitosis and, perhaps more so, of the mitosis/apoptosis ratio, which will lead to such an abnormal large mass [12].

In normal cells, processes such as DNA replication, DNA transcription and RNA translation convert molecular binding energy, chemical bond hydrolysis and electric gradients into mechanical work, related to conformational changes and displacements [13]. Still, the origin of this mechanical conversion of energy is not yet completely understood; as such, a better insight into the signaling pathways that process cell proliferation and also into the mitosis/apoptosis ratio could lead to new therapeutic approaches to diseases, particularly with regard to cancer [11].

Recently, an entropy generation concept based on the Gouy–Stodola theorem [14] has been suggested as a powerful approach to analyze not only the cells' biochemical and biophysical processes [8–10], but also their statistical and chemo-thermodynamic pathways [11,15].

The aim of this paper is to introduce this approach to the mitosis/apoptosis ratio in an effort to obtain a new method of analysis for these processes, and to suggest implementing an external field as novel treatment modality in support of currently applied anticancer regimen. To do so, in Section 2, a summary of the thermodynamic approach is presented, while, in Section 3, it will be discussed from a biomedical point of view. This is followed by Section 4, which presents relevant *in vitro*, *in vivo* and *clinical* data from the literature prior to concluding remarks summarizing our findings, both theoretically and experimentally.

2. The thermodynamic approach

In this section, we summarize some recent thermodynamic results that are useful to develop the biomedical arguments.

In applied thermodynamics, the quantitative description of irreversibility is obtained by introducing the concept of entropy generation. Cells are open and complex systems, and, as such, they can be analyzed by using an applied thermodynamics approach. Consequently, it can be useful to understand the thermodynamic bases of self-organization within the realm of the evolution of order and life [8]. First, the entropy generation of any open system is defined as [16]:

$$S_g = \int_0^{\tau} \left[\frac{\mathrm{d}S}{\mathrm{d}\tau} - \sum_{i=1}^{n} \frac{\dot{Q}_i}{T_i} - \sum_{in} G_{in} s_{in} + \sum_{out} G_{out} s_{out} \right] \mathrm{d}\tau \tag{1}$$

where τ is the lifetime of the process, which can be defined as the range of time in which the process occurs [9,14,15]; Q stands for the heat exchanged, T is the temperature of the thermal source, s represents the specific entropy and G is the mass flow. In relation to cells, the entropy generation has recently been evaluated as [8]:

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

where:

1. $S_{g,tf}$ is the entropy generation due to the thermal flux driven by temperature difference, which was obtained as $S_{g,tf} \approx \frac{uL^2 \dot{x}_{th}}{6T^2} \Delta T \tau_1$.
2. $S_{g,dc}$ is the entropy generation due to the diffusion current driven by chemical potential gradients, which was obtained as $S_{g,dc} \approx \frac{\dot{x}_{th} V_m}{T} \frac{\sum_i \rho_i (\mu_{i,os} - \mu_{i,is})}{d_m} \tau_2$.
3. $S_{g,vg}$ is the entropy generation due to the velocity gradient coupled with viscous stress, which was obtained as $S_{g,vg} \approx \frac{4\pi}{T} \eta \frac{\dot{\mathbf{x}}_B^2}{r d_e} \tau_3$.
4. $S_{g,cr}$ is the entropy generation due to the chemical reaction rate driven by affinity, $S_{g,cr} \approx V \tau_4 \sum_i N_i \frac{\mathcal{A}_i}{T}$.
5. $S_{g,de}$ is the entropy generation due to the dissipation generated by interaction with the environment which was obtained as $S_{g,de} \approx -\int_V \mathrm{d}V \int_0^{\tau_5} \frac{v}{T} \sum_k \mathbf{J}_k \cdot \mathbf{F}_k$.