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Entropy Production, Entropy Generation, and Fokker-Planck Equations for Cancer Cell Growth

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Abstract: It is rather difficult to understand biological systems from a physics point of view, and understanding systems such as cancer is even more challenging. There are many factors affecting the dynamics of a cancer cell, and they can be understood approximately. We can apply the principles of non-equilibrium statistical mechanics and thermodynamics to have a greater understanding of such systems. Very much like other systems, living systems also transform energy and matter during metabolism, and according to the First Law of Thermodynamics, this could be described as a capacity to transform energy in a controlled way. The properties of cancer cells are different from regular cells. Cancer is a name used for a set of malignant cells that lost control over normal growth. Cancer can be described as an open, complex, dynamic, and self-organizing system. Cancer is considered as a non-linear dynamic system, which can be explained to a good degree using techniques from non-equilibrium statistical mechanics and thermodynamics. We will also look at such a system through its entropy due to to the interaction with the environment and within the system itself. Here, we have studied the entropy generation versus the entropy production approach, and have calculated the entropy of growth of cancer cells using Fokker-Planck equations.

Keywords: Fokker-Planck equations; non-equilibrium statistical mechanics; entropy

1. Introduction

The Physics of Living Systems Community has collectively become excited by the possibility of gaining a better understanding of and better treatment options for cancer [1]. There has been a considerable rise in the number of studies in which the principles of physics and related fields can be applied to understand cancer and seek detection methods and better treatment scenarios. This interdisciplinary field has been very active in the last decade or so, and the scientific community has contributed considerably towards this goal. The question which arises is, "How does physics apply to biological systems"? One of the many answers to this question is that the fundamentals of cancer are the fundamentals of growth [2]. Physics offers tools and techniques to understand and attack the process of disease from a very fundamental level. One such tool in physics used in biological systems is the application of non-equilibrium physics. If we consider systems which are small, we cannot apply standard equilibrium physics techniques. In such systems, statistical fluctuations become very significant, and recent advances have shown that these fluctuations satisfy their own laws [3]. This is where non-equilibrium physics can explain the phenomena. There have been numerous studies which suggest that the growth of cancer cells are not linear with time, and follow a very complex mechanism. This means that the growth of cancer cells cannot be explained without taking into account the aspects of non-equilibrium statistical physics, in addition to the study of fluctuations in complex systems [4]. In this context, the Fokker-Planck equation is a good tool, as it represents the probability density for

the position or velocity of a particle of which the motion is described by a corresponding Langevin equation [5]. Since the entropy of a system always increases, the Fokker-Planck equation can be used to calculate the entropy of the growth of cancer cells. This paper discusses the entropy generation and entropy production approach to calculating the entropy of the non-equilibrium growth of cancer cells.

2. Non-Equilibrium Fokker-Planck Equations

Consider a set of n interacting particles. Let the particles evolve with time through the Langevin equations given by

$$\frac{dx_i}{dt} = f_i(\mathbf{x}) + r_i(t), \tag{1}$$

where x_i is the position of the ith particle, $\mathbf{x} = \{x_i\}$, $f_i(\mathbf{x})$ is the force acting on the ith particle, and r_i is the noise that is mathematically considered to be a stochastic variable, such that

$$\langle r_i(t) \rangle = 0 \tag{2}$$

$$\langle r_i(t) r_j(t') \rangle = 2D_i \delta_{ij} \delta(t - t') \tag{3}$$

with $D_i \geq 0$, different constants for each particle. The associated Fokker-Planck equations describe how the probability distribution, $P(\mathbf{x}, t)$ evolves with time [6]. This can be written as

$$\frac{\partial P(\mathbf{x}, t)}{\partial t} = -\sum \frac{\partial}{\partial x_i}[f_i(\mathbf{x}) P(\mathbf{x}, t)] + \sum D_i \frac{\partial^2}{\partial x_i^2} P(\mathbf{x}, t). \tag{4}$$

We can write down the Fokker-Planck equation in a more convenient way as a continuity equation,

$$\frac{\partial P(\mathbf{x}, t)}{\partial t} = -\sum \frac{\partial}{\partial x_i} J_i(\mathbf{x}, t) \tag{5}$$

$$J_i(\mathbf{x}, t) = [f_i(\mathbf{x}) - D_i \frac{\partial}{\partial x_i}] P(\mathbf{x}, t), \tag{6}$$

where J_i is the ith component of the current of probability. The condition of irreversibility can be expressed as

$$D_i \neq D_j, i \neq j,$$

or

$$D_i = D_j = D, i \neq j,$$

but

$$\frac{\partial f_j}{\partial x_i} \neq \frac{\partial f_i}{\partial x_j}. \tag{7}$$

The Fokker-Planck equation has to be solved inside a given region of the space spanned by the set of variables x_i subject to a prescribed boundary condition which governs the behavior of $P(\mathbf{x}, t)$ and $J_i(\mathbf{x}, t)$. In the thermodynamic equilibrium case, the Langevin equation and the associated Fokker-Planck equations describe a system where

$$\frac{\partial f_j}{\partial x_i} = \frac{\partial f_i}{\partial x_j}$$

for any pair, i and j, and

$$D_i = D_j. \tag{8}$$

3. Entropy Production and Fokker-Planck Equations

Cancer cell growth can be considered as an irreversible system, and there is a continuous production of entropy in such systems. The rate of change of the entropy S of a system can be written as [7]

$$\frac{dS}{dt} = \varsigma - \Omega, \tag{9}$$

where ς is the entropy production due to irreversible processes in the system and Ω is the entropy flux from the system to the environment. In an equilibrium system, entropy is a well-defined quantity, but in non-equilibrium systems, the entropy, as well as the production of entropy, is not well-defined. Since a non-equilibrium system is defined by the Fokker-Planck equations, we have hence attempted to calculate the production of entropy in such systems. The Gibbs entropy of a system at any time, t, is given by [6,8–10].

$$S(t) = -\int P(\mathbf{x},t)\; ln[P(\mathbf{x},t)]\; d\mathbf{x} \tag{10}$$

where $d\mathbf{x} = dx_1 dx_2 \cdots dx_n$. Using Equation (5), we can express the derivative of the entropy as

$$\frac{d}{dt}S(t) = -\int [lnP(\mathbf{x},t) + 1] \sum \frac{\partial}{\partial x_i} J_i(\mathbf{x},t)\; d\mathbf{x}. \tag{11}$$

Integrating it, we get

$$\frac{d}{dt}S(t) = -\int \sum J_i(\mathbf{x},t)\; \frac{\partial}{\partial x_i} lnP(\mathbf{x},t)\; d\mathbf{x}, \tag{12}$$

and using Equation (6), we can write

$$\frac{d}{dt}S(t) = -\int \sum \frac{1}{D_i}\; J_i(\mathbf{x},t)\; f_i(\mathbf{x})\; d\mathbf{x} + \int \sum \frac{[J_i(\mathbf{x},t)]^2}{D_i P(\mathbf{x},t)}\; d\mathbf{x}. \tag{13}$$

Comparing this with Equation (9), we see that

$$\Omega = \int \sum \frac{1}{D_i}\; J_i(\mathbf{x},t)\; f_i(\mathbf{x})\; d\mathbf{x} \tag{14}$$

and

$$\varsigma = \int \sum \frac{[J_i(\mathbf{x},t)]^2}{D_i P(\mathbf{x},t)}\; d\mathbf{x}. \tag{15}$$

Using Equation (6), we can write Equation (14) as

$$\Omega = \int \sum \left\{ \frac{1}{D_i}\; [f_i(\mathbf{x})]^2 + f_{ii}(\mathbf{x}) \right\}\; P(\mathbf{x},t)\; d\mathbf{x}, \tag{16}$$

where $f_{ii}(\mathbf{x}) = \frac{\partial f_i(\mathbf{x})}{\partial x_i}$. This can be expressed as an average over the probability distribution.

$$\Omega = \langle \sum \left\{ \frac{1}{D_i} [f_i(\mathbf{x})]^2 + f_{ii}(\mathbf{x}) \right\} \rangle \tag{17}$$

There is another study of the total entropy production [11,12]. The authors clearly mentioned that the the total entropy production (EP) $\dot{S}_{tot}$ is the sum of two constitutive parts—namely, the so-called adiabatic $\dot{S}_a$ and non-adiabatic $\dot{S}_{na}$ contribution. Each of these entropies cannot be less than zero.

4. Entropy Generation and Fokker-Planck Equations

It has been discussed by Jaynes that Gibbs' formalism for statistical physics of systems under an equilibrium can be understood as a generalized form in a statistical inference theory for non-equilibrium systems [13]. Jaynes developed non-equilibrium statistical physics for the stationary state constraint on the basis of maximum entropy, and his approach consisted of maximizing the path. The Shannon information entropy for the path can be written as

$$S = -\sum_{\gamma} p_\gamma ln(p_\gamma), \tag{18}$$

with respect to p_γ of the path γ. According to Shannon, the information entropy can be written as the logarithm of the number of outcomes i with non-negligible probability p_i, while in non-equilibrium statistical physics, it is given as the logarithm of the number of microscopic phase-space paths γ having non-negligible probability p_γ [5,13]. Following this approach, we know that the information entropy for open systems is related to their entropy generation by [14–16]:

$$S_g = \kappa_B S = -\kappa_B \int P_\gamma(\mathbf{x}, t) ln[P_\gamma(\mathbf{x}, t)] d\mathbf{x} \tag{19}$$

with $p_\gamma = P_\gamma(\mathbf{x}, t)$. This relation is the statistical definition of entropy generation. This can also be explained as the missing information which is necessary for predicting which path a system of the ensemble takes during the transition from one state to another. The Guoy-Stodola theorem [5] gives

$$\bar{W} = T_0 S_g, \tag{20}$$

where $\bar{W}$ is work lost due to internal irreversibility in a system. By definition, entropy generation can be related to the power lost, where P is due to irreversibility,

$$S_g = \frac{1}{T_0} \int_0^\tau P dt \tag{21}$$

and T_0 is the environmental temperature—considered constant—and τ is the time duration of a physical process. The power lost by definition is given as:

$$P = \langle \sum f_i(\mathbf{x}) \frac{dx_i}{dt} \rangle. \tag{22}$$

Using the Langevin equation, we can write this as

$$P = \langle \sum f_i(\mathbf{x}) [f_i(\mathbf{x}) + r_i(t)] \rangle, \tag{23}$$

and so S_g can be written as

$$S_g = \frac{\tau}{T_0} \langle \sum ([f_i(\mathbf{x})]^2 + D_i f_{ii}(\mathbf{x})) \rangle, \tag{24}$$

where $f_{ii} = \frac{\partial f_i}{\partial x_i}$. Considering the mean value, we can finally write this as

$$S_g = \frac{\tau}{T_0} \int \sum ([f_i(\mathbf{x})]^2 + D_i f_{ii}(\mathbf{x})) P_\gamma(\mathbf{x}, t) d\mathbf{x}, \tag{25}$$

and hence,

$$S_g = \frac{\tau}{T_0} \int \sum f_i(\mathbf{x}) J_i(\mathbf{x}, t)\, d\mathbf{x}, \tag{26}$$

where the last term is related to the Fokker-Planck equation.

5. A Generalized Model for Cancer Growth

Cell adhesion is essential in all aspects of cell growth, cell migration, and cell differentiation. Cellular adhesion molecules (CAMs) are important participants in cell–cell interactions, as well as interactions between cells and components of the extra-cellular matrix [17,18]. We assumed that as cancer cells start to grow and multiply, the inter-cellular force between them is strong enough to sustain growth, and they would also exhibit a London dispersion force-like term [19]. We assumed a London-type force because we would have liked to express the interaction between two cancer cells to mimic a London dispersion-like force. In addition, we assume that the growth of cancer cells is exponential. Based on this understanding, our assumption of the force term can be written as

$$f_i(r) = \frac{\exp(-\alpha r)}{(\beta r^6 + \delta)}, \tag{27}$$

where α, β, and δ are constants related to the strength of the force.

For the entropy production approach, using the force term, we can write Equation (17) as

$$\Omega = \langle \left\{ \frac{1}{D} \frac{\exp(-2\alpha r)}{(\beta r^6 + \delta)^2} - \frac{\exp(-\alpha r)}{(\beta r^6 + \delta)} [\alpha + \frac{6br^5}{(\beta r^6 + \delta)}] \right\} \rangle. \tag{28}$$

Also, Equation (6) can be written as

$$J(r, t) = [\frac{\exp(-\alpha r)}{(\beta r^6 + \delta)} - D\frac{\partial}{\partial r}] P(r, t), \tag{29}$$

and we can write Equation (14) as

$$\varsigma = \frac{1}{D} \int \frac{[[\frac{\exp(-\alpha r)}{(\beta r^6 + \delta)} - D\frac{\partial}{\partial r}] P(r, t)]^2}{P(r, t)}\, dr. \tag{30}$$

Finally, we can express Equation (9) as

$$\frac{dS}{dt} = \frac{1}{D} \int \frac{[[\frac{\exp(-\alpha r)}{(\beta r^6 + \delta)} - D\frac{\partial}{\partial r}] P(r, t)]^2}{P(r, t)}\, dr \; - \; \langle \left\{ \frac{1}{D} \frac{\exp(-2\alpha r)}{(\beta r^6 + \delta)^2} - \frac{\exp(-\alpha r)}{(\beta r^6 + \delta)} [\alpha + \frac{6br^5}{(\beta r^6 + \delta)}] \right\} \rangle. \tag{31}$$

Similarly, for the entropy generation approach, we can express Equation (26) as

$$S_g = \frac{\tau}{T_0} \int \left\{ \frac{\exp(-2\alpha r)}{(\beta r^6 + \delta)^2} - D\frac{\exp(-\alpha r)}{(\beta r^6 + \delta)} [\alpha + \frac{6br^5}{(\beta r^6 + \delta)}] \right\} P_\gamma(r, t) dr. \tag{32}$$

Since this is a model independent study of the entropy of cancer cells, in Figure 1, we plot Equation (31) as an example. The values of the constants α, β, δ, D are taken to be one for simplicity. Δr, which is assumed to be the separation of two cancer cells, was approximated based on the size

of a typical cancer cell. We have taken only a small range of values to show how $\frac{dS}{dt}$ progresses [20]. As expected, $\frac{dS}{dt}$ increases with Δr.

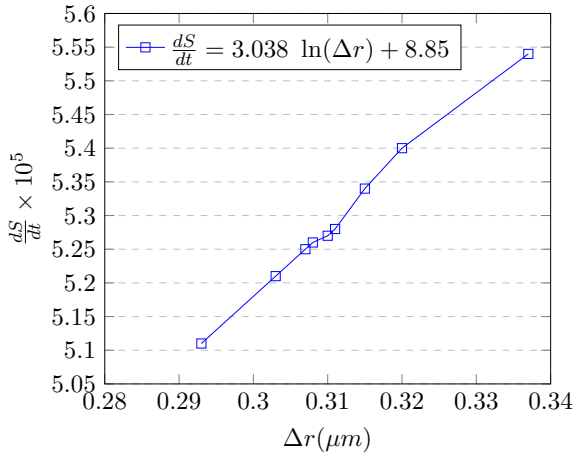

Figure 1. A display of $\frac{dS}{dt}$ as in Equation (31) versus Δr. The constants α, β, δ, D =1. The probability distribution function has been maximized so that we can get the maximum change in entropy as time changes.

6. Conclusions

In this paper, we have expressed the entropy terms of cancer cell growth by applying the entropy production and entropy generation approaches. The principles of statistical physics allow a connection between the Fokker-Planck equations and both of these approaches. Based on the properties of cell-to-cell interaction and of adhesion, our approach was to understand what type of force would facilitate the growth of a cancer cell. This study was based on a model independent approach where we have tried to explain the growth of cancer cells and how it can be connected to entropy calculations. Based on this, we have made basic assumptions about what a cancer cell growth force equation may look like. Finally, we have shown through Equations (27) through (32) a procedure to calculate the entropy given the probability distribution.

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References

1. Levine, H. Introduction to physics in cancer research. *Cancer Res.* **2014**, *74*, 4572. [CrossRef] [PubMed]
2. Solomon, K.A. Physics and cancer. *Phys. Today* **2002**, *55*. [CrossRef]
3. Klopper, A. Topics in non-equilibrium physics. *Nat. Phys. Insight* **2015**, *11*. [CrossRef]
4. Jordan, R.; Kinderlehrer, D.; Otto, F. The variational formulation of the fokker-planck equation. *SIAM J. Math. Anal.* **1996**, *29*, 1. [CrossRef]
5. Lucia, U. Entropy generation and the fokker-planck equation. *Physics A* **2014**, *393*, 256. [CrossRef]
6. Tome, T. Entropy production in nonequilibrium systems described by a Fokker-Planck equation. *Braz. J. Phys.* **2006**, *36*, 1285. [CrossRef]
7. Nicolas, G.; Prigogine, I. *Self-Organization in Nonequilibrium Systems*; Wiley: New York, NY, USA, 1977.
8. Tome, T.; DeOliviera, M.J.T. Entropy production in irreversible systems described by a Fokker-Planck equation. *Phys. Rev. E* **2010**, *82*, 021120. [CrossRef] [PubMed]
9. Tome, T.; DeOliviera, M.J.T. Entropy Production in Nonequilibrium Systems at Stationary States. *Phys. Rev. Lett.* **2012**, *108*, 020601. [CrossRef] [PubMed]

10. Tome, T.; DeOliviera, M.J.T. Stochastic approach to equilibrium and nonequilibrium thermodynamics. *Phys. Rev. E* **2015**, *91*, 042140. [CrossRef] [PubMed]
11. Esposito, M.; Van den Broeck, C. Three faces of the second law. I. Master equation formulation. *Phys. Rev. E* **2010**, *82*, 011143. [CrossRef] [PubMed]
12. Van den Broeck, C.; Esposito, M. Three faces of the second law. II. Fokker-Planck formulation. *Phys. Rev. E* **2010**, *82*, 011144. [CrossRef] [PubMed]
13. Dewar, R. Information theory explanation of the fluctuation theorem, maximum entropy production and self-organized criticality in non-equilibrium stationary states. *J. Phys. A Math. Gen.* **2003**, *36*, 631. [CrossRef]
14. Lucia, U. Statistical approach of the irreversible entropy variation. *Phys. A Stat. Mech. Appl.* **2008**, *387*, 3454–3460. [CrossRef]
15. Lucia, U. Irreversibility, entropy and incomplete information. *Phys. A Stat. Mech. Appl.* **2009**, *388*, 4025–4033. [CrossRef]
16. Lucia, U. Maximum entropy generation and κ-exponential model. *Phys. A Stat. Mech. Appl.* **2010**, *389*, 4558–4563. [CrossRef]
17. Cohen, M.; Grieblin, T.; Ahaghotu, C.; Rokhlin, O.; Ross, J. Cellular adhesion molecules in urologic malignancies. *Am. J. Clin. Pathol.* **1997**, *107*, 56–63. [CrossRef] [PubMed]
18. Okegawa, T.; Pong, R.; Li, Y.; Hsieh, J.T. The role of cell adhesion molecule in cancer progression and its application in cancer therapy. *Acta Biochim. Pol.* **2004**, *51*, 445. [PubMed]
19. London, F. The general theory of molecular forces. *Trans. Faraday Soc.* **1937**, *33*, 8b. [CrossRef]
20. Iyer, S.; Gaikwad, R.M.; Subba-Rao, V.; Woodworth, C.D.; Sokolov, I. Atomic force microscopy detects differences in the surface brush of normal and cancerous cells. *Nat. Nanotechnol.* **2009**, *4*, 389–393. [CrossRef] [PubMed]