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# The Growth of Healthy and Cancerous Tissues

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## Abstract

The structure of the tissues is formed in a self-similar manner, forming fractal structures in their transport networks. The structure exhibits allometric forming and so-called scaling behavior. This is a basic growth model fine-tuned by various connections of the cells (junctions and adherent connections), intended to direct material and energy transports between them. This secondary control of cell metabolism decreases primary metabolic transport through the free surfaces of the cells. The cellular network is formed by triggering the endogenous electric fields, which are dominantly governed by cell membrane potential. Proliferation exhibits a different electric pattern due to the low cell-membrane potential and resulting negativity relative to its environment. This potential change characterizes cells in normal proliferation and a cluster of cells (a tumor) in the case of cancerous development. This latter has certain similarities to the leakage transport of liquid in porous media, substituting the pressure with endogenous tumor potential. The average survival of a tumor depends on the kind of available metabolic transport and the fractal dimensions of the newly built angiogenic network.

## Keywords

Endogenous Potential, Metabolic Scaling, Competition, Cooperation, Self-Time, Tumor Survival

## 1. Introduction

The form of various organs is evolving in the early stage of the development of the complete body. The evolution of mass of the organ roughly keeps the form-similarity until the adulthood of the subject. The question is automatically arising: how the organ grows? We convinced having only one pivotal orientation appears, the bioscaling [1], and the connected ontogenic growth [2], if it is valid

for the individual organs [3]. In this assumption, we have two consequences:

- The network of the blood-flow in the organ follows the complete network of the body in its structure and organizing,
- The network in the organ is optimized, suitable for the largest available transfer of materials and energy flow.

When dividing the organ on small, tightly connected, space-filling elementary cubes, we may assume that every cube grows isotropic way. The same number of cells is born and dies by apoptosis in average in every cube. Consequently, the linear size of the organ changes by the  $1/3$  power of time. This model is the equally distributed production of cell numbers. All the cube-elements have the same mass-balance, which has production and annihilation elements (mainly apoptosis) are equal in average in every cube.

There are originally two categories of cells existing by their behaviour: collective and non-collective. The cells in solid malignant tumor usually are non-collective. They are normally autonomic and competing for each other for the necessary nutrients. In the healthy development of the tissue, the cells are cooperative, and this cooperation determines their structural properties. We may assume in healthy cases that every “elementary cube” described above has the same metabolic conditions, [2]; the material transfer for the metabolism, in general, is optimized.

The circulation network is organized by fractal geometry [4], which is based on the unified self-similar construction of the nets. This is a space-filling isotropic growth model with simple steps of building: continuing with the same template at every terminal. Due to this construction procedure, the metabolic rate depends on the  $3/4$  power of the mass of the given volume [5].

Our goal is to show how the malignant growth modifies the normal healthy growth of the tissue.

## 2. Character of the Cell-Fission

The organ is a set of cells that “democratically” consumes the optimal amount of materials and energy from the network. However, this situation is approximate only. The fractal-network of the vessels, which ensures the distribution is not enough alone to provide the satisfactory info and material-exchange. Therefore, cells form a secondary network of junctions and adherent connections between them, making an additional distribution. These cellular connections make such corrective actions, which guarantee the optimal distribution of the “resources” between the cells. The secondary network needs a part of the membrane surface, decreases the original effective free surface of the cells, decreasing the transport facility forms of the primary network. Accordingly, the self-similar fractal network is not enough for the information exchange and the system forces to generate the secondary networks of the cellular connections. The possible exchange of molecules through the junctions specifies the correction of metabolic processes which is the extension of the primary transport-networks. As well as this secondary (adhesion) structure guarantees the mechanical structure of the

organ, even it keeps the cells together in its ex-vivo states too.

The logical assumption is that the growth of the consequent effective surface of the cells in a specific organ is proportional to the effective surface of capillaries ( $a$ ) available for the material transfer. When  $N_c$  is the actual number of cells, and  $a_c$  is the effective surface of a cell for metabolic activity, which depends on its environmental population (depends of  $N_c$ ), so  $a_c = a_c(N_c)$ , and  $N_c \cdot a_c(N_c)$  is the effective surface of the input of a single cell, which is of course is limited by the availability of the complete supply ( $a$ ), so:

$$a \leq N_c \cdot a_c(N_c) \quad (1)$$

We have shown elsewhere [6] that the metabolic rate depends on not only the mass but on the linear size of the circulation length by 3/4 power, too, and the actual average mass ( $m$ ) and the actual average length of the blood circulatory network, ( $l$ ), related as:

$$m \propto Kl^4 \quad (2)$$

where  $K$  is a constant, and  $N_c \propto m$ .  $m \propto L^3$ , where  $L$  is the linear size of the given organ. Using (1) and (2) in case of optimal equality we obtain:

$$l^3 \propto l^4 a_c(N_c) \rightarrow a_c \propto l^{-1} \propto L^{-3/4} \quad (3)$$

Consequently, the effective surface of a cell cannot decrease more intensive than the  $-3/4$  power of the linear size of the organ. Hence the effective membrane surface is inversely proportional to the length of the organ, so the size of the growth of the organ allows more possibilities to build up a secondary network between the cells. This has further consequences: when the cell would be able to terminate its secondary network, it will do it because the growth of its active surface allows more metabolic influx. The survival on the cellular level has higher priority for the cell than its organism level.

When the cell division starts, grows its metabolic demand. It needs more energy and material transport than was before, and so the cell increases its demand of metabolic transfer directly through its membrane. It must isolate itself from the network, it tries to reach the autonomy, terminates the surface-limiting connections to neighboring cells. The autonomy of the cells requests a new decision of the fate of it when the division is over, and the two autonomic daughter cells appear. The termination of the networking in this line is an energetic constraint. This well explains the forming of  $\alpha$ -state [7]. In the case of cancer-state of the cell, the terminated collectivity is one of the factors to fulfill the high metabolic request of permanent growth.

Building up a structure needs stability. The stable state in the level of forces means a stationer equilibrium of the attractive and repulsive forces. Do these forces act in the case of tissues? Yes, these exist in the structure of the tissue. The attractive force is the collectivity. The distance of cellular communication defined by different signaling mechanisms [8], including the intracellular, the information exchange between neighboring cells, as well as short distance communication (e.g. synapses), and long-distance communications by various hor-

mones and molecules, including exosomes and other vehicles. Research on signaling (social signals) of cells [9] and the pathways of cell-communication are in the focus of emerging attention [10].

There is an attraction between the identical collective cells even from the distance of  $\approx 1 - 4 \mu\text{m}$ , [11]. Such long-range interaction could be explained by resonances and super-polarization [12]. The repulsive force which balances the attraction is the membrane polarization; the outside membrane-wall is positive, which repulses the individual cells. The repulsion is crucial in living structures because the material and energy-transport need free surfaces between the cells. The process of decrease in the membrane potential is parallel with the decline in the collective status of the cell.

The formation of the structures has a variation of the symmetries frequently showing 6-fold and 5-fold arrangements. This symmetry-forming is well known in the non-living environment too, [13]. However, the formation of organs is thermodynamically very different from the crystallization of the non-living objects. In the crystallization process heat is liberated permanently because of the crystal-structure forms by the ordering of the disordered material. Consequently, entropy is produced, which must be liberated from the system. The entropy leaves the system by the internal energy flow, heat appears, when the crystallization happens. This mechanism needs a free surface, so the entropy current is limited by the availability of the surface. The information change in living systems is much more than at the crystallization in non-living. A particular temperature does not fix in the living organization, it happens at a wide range of temperature interval, and no permanent cooling is necessary for this organizing process; with another way of entropy decreasing. The entropy-decrease is probably sunk by the order-disorder transition of the aqueous solution; the structured water takes the entropy by its disordering. Without this order-disorder transition of the water, no ordering of the cells could happen. During the organizing process of the cells its structured water transforms to disordered, the water concentration decreases in the cytoplasm, so its resting potential will be higher. Only the cells with resting potential and with ordered water in their interior can be organized. The problem of the cancerous cells is that practically they have no ordered water, which could take the entropy of the ordering transition of the cell. When this primary ordering is not able to be performed, the polymerization forming of the cytoskeleton is also blocked.

The energy minima derive the actual arrangement of the non-living structures. Contrary, the living ones prefer the symmetries depending on the real role of the collectivity of the cells. The structures which must have small hydraulic resistance for transfers will arrange mostly pentagonal (five-fold) symmetry which has "lazy" space filling, allow free space for transfers [14]. However, when the surface energy should be minimized, the 6-fold, hexagonal structure forms.

The above forming symmetry well explained by the Dirichlet theorem of minimizing the electrostatic energy, [15]. Consider the cells conductive, having resting potential (70 - 100 mV). There is neutral (having the same amount of

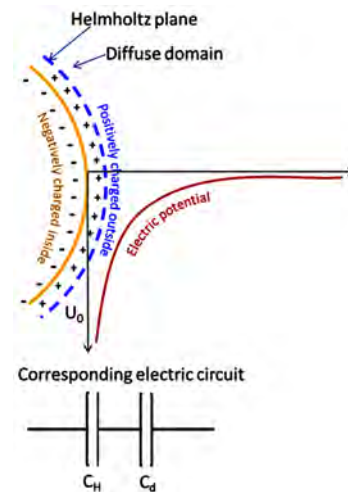
positive and negative ions) electrolyte between the cells. However, the equilibrium ion-distribution of the extracellular electrolyte changes nearby the cells, electric double-layer forms, **Figure 1**. The substitutional circuit on discrete capacitors was worked out in details [16].

The tissue contains a network of capacitors, as many parallel circuits as the number of cells in **Figure 2**.

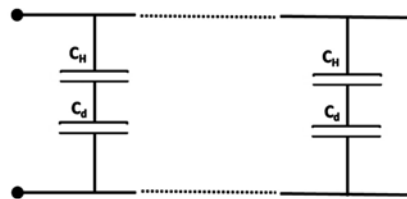
According to the Dirichlet theorem, the electrostatic energy has its minimum in the equilibrium phase. The energy could be minimized, when the complete, consequent capacity of the system in **Figure 2** is minimal. The capacity depends on the permittivity of the material between the electrodes and the geometry of the electrode arrangement. Knowing that the thickness of the double layer and inter-distance of the cells are much less than the size of the cell, the condensers could be regarded as planar, so

$$\frac{A}{d} \quad (4)$$

where  $A$  is the value of the surface, and  $d$  is the distances of the cells (electrodes of the capacitors). The coagulation of the cells is inhibited by their surface charges. Consequently, the minimizing of the consequent capacity could happen by the minimizing of the actual surfaces or maximize the distances. In the case of a hexagonal arrangement, the surface would be kept to a minimum; however, with a pentagonal structure thickness increases. Which solution is realized depends on the actual function of the arrangement.



**Figure 1.** Distribution of charge and potential near the boundary of the cell.



**Figure 2.** Electric substitutional picture of the tissue.

The physics of the tissue forming in this picture is very like the stability conditions of the colloidal solutions. This description well fits to the early evolution, when the coagulation is prohibited, and the free-space between the cells was governed by the metabolic transports. The formed distances depended on the shape, resting potential, charge-conditions, etc.

The above description models some tendencies but cannot explain the forming of the tissue by mostly repulsive interactions. The opposite (attractive) forces have to be involved for more realistic description. This request is like the forming of non-living structures, but the non-living explanations could not be adequate to the active living state. One of the guiding rules of the non-living world is the tendency to make energy-minima. For example, the crystals show this rule. The crystals, however, have no unique forms; they could have very different crystalline structures. All the crystalline structures obey the minimal energy rule; however, various tissues form in the living cell based on the nature of that particular organ. The organs have appropriate forms and their size growth by time. The tissue structure of the organs also has an identity; their cells form the tissues of the organs with the unified architecture. By the growing of the subject, the architecture grows too, but the shape is conserved. The form of the organ, tissue, and cells could not be explained by physical interaction mechanisms alone. The form must be functional. The functional architecture probable was formed successively by the evolution, and the mutations, the selection and their information fixed in the DNA developed the self-replication basic mechanisms.

The function of the cell is determined by its position in the tissue, so probably two identical cells do not exist. The cell has adaptability and differentiability making it suitable for the actual function of the actual position. The cell behaves differently when the conditions change. In this meaning, it is well like a logical electric circuit. The basic discrete elements are equivalent, but their function differs according to their actual position in the circuit. Its actual environment determines the differentiation of the cell. The environment by its physical and chemical inputs reprograms the cellular function, fixing it in the DNA. This also means that certain useless functions are blocked. The newly born cell inherits this block. This is the microscopic evolution realizing the function of the cell in the organ according to its position. The macro-differentiation develops the basic cells of the organs.

The growth of the organ keeps the geometric similarity, accompanied by the fixed density in actual place of the organ. Probable the structure does not change inside of the organ while it is healthy, hence the cell-fission is homogeneous ligands, and division promoters distribute homogeneously in, they have gradient only at the boundary of the organ.

### **3. Growth of a Tumor and Its Average Survival Time**

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The ratio of  $l$ , and the asymptotic length of completed network ( $l_0$ ), equal with the ratio of  $m$  and the asymptotic mass ( $m_0$ ) on the  $1/4$  power, so

$$\left(\frac{m}{M}\right)^{1/4} = \frac{l}{l_0} = \lambda \quad (5)$$

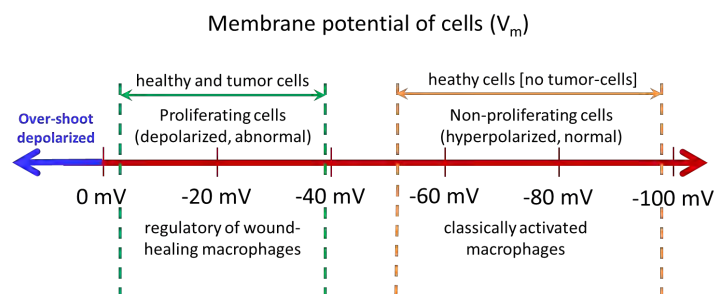
Consequently, the average  $l$  length of the network may be chosen as growth factor. We may introduce the biological self-time by

$$\begin{aligned} \lambda(\tau) &= 1 - e^{-\tau} \\ \tau &= at/4M^{1/4} - \ln(1 - \lambda_0) \end{aligned} \quad (6)$$

where  $\lambda_0$  is the ratio of the just-born mass to the asymptotic (completed, final) mass, and  $\tau$  is the self-time. This well corresponds with the measurements, [17]. Every similar network has same biological self-time.

The normal reaction to injury is to improve the cellular proliferation replacing the damaged cells and heal the wound. The membrane potential of these newly proliferation cells is also significantly lower than the cell membrane potential of healthy mature cells [18]. After maturing of the daughter cells, their membrane-potential grow again to the healthy character. However, in cancerous proliferation, such return does not happen. The mineral contents of the cancerous cells are robustly changed which has role keeping the cell-membrane potential low, [18] [19] [20], especially an increase in the intracellular concentration of positively charged ions and an increase in negative charges on the glycocalyx coat of the cell. Together with the lower electrical membrane potentials cancer cells have lower electrical impedance than normal cells [20] [21] [22].

The membrane potentials of proliferating cells are certainly lower, irrespective that these are malignant or normal processes [23] [24], as well as the macrophages seeking to repair the broken arrangements changes its membrane potential is not repulsed by the irregularly depolarized, out of network cooperation cells [25] **Figure 3**.



**Figure 3.** Membrane potentials of networked and proliferating cells are forming two distinct groups. The proliferation (irrespective that it is healthy or malignant) is always depolarized. Eg. the fertilized egg has approximately the same membrane potential ( $V_m$ ) than the ovarian tumour-cells; mouse hepatoma cells have approx. the same  $V_m$  than the human one; proliferating fibroblasts and fibrosarcoma have also approx.. same  $V_m$ .

Therefore, a key component of cell repair and cancer treatment would be to re-establish a healthy membrane potential in the body's cells [26] [27]. The external oscillating electric field in the extracellular electrolyte can adversely affect and support the growth of the membrane potential, [28] [29]. This is one of the factors of modulated electrohyperthermia (mEHT, trade name oncothermia) [30] [31].

#### **4. Growth of the Healthy Tissues, Competition for Nutrients**

The mechanisms of the growth of the cellular clusters are very similar for cancerous and healthy embryonal cases. The huge difference, however, in their boundary conditions. A tumor grows dominantly on its surface, while the growth of normal embryo is certainly volumetric. Consequently, the supportive transport network has different fractal structure.

The embryonic growth of healthy organ performs cell division on any points of the organ volume. This growth results in embryonic cells, sharing the same terminal of the blood-vessel network as the mother cell had originally. Due to the relative negative surface (lowered positive charges) of the embryonal cells, a potential gradient will induce currents activation the VEGF receptors, triggering the directed growth of the transport network to serve them [32]. During the transition time, until the generation of the new blood vessels, the diffusion transports the nutrients, governed by the concentration gradients. Note, that the physiological electric fields can generate not only neo-vascular growth but directional nerve development as well [33]. The triggering and control of the construction of various networks in the living systems could be well organized by endogenous electric signals [34]. These processes belong to the category of diffusion-limited aggregation (DLA), like the electric field of dielectric breakdown production too [35]. The DLA processes produce branching pattern fractal network [36].

The process of growing number of cells is not a competition; it is the repetition on the same physiological principle in all steps of the development. The process is stable because the mature cell stops the triggering. The primary embryonal cell starts the forming of its network (electric field triggering, like a template) and this micro-process repeated identically, constructs the self-similar structure, serving the formed network with well-supplied blood.

#### **5. Growth of Cancer**

The cancerous set of cells has in principle infinite ability of growth. This agglomerate is more negative in its charge than the healthy surrounding because the individual cells are negatives. This macroscopic cluster similarly triggers the growth of blood-supply as the individual embryonic cell, but this is now macroscopic. The growth of this macroscopic set of cells is surface controlled, (the surface of the cluster grows), while the embryonic process is volume controlled by microscopic source. Consequently, despite the applied same physio-

logical principle the branching pattern and so the fractal dimension will be different. In the case of cancer, the layers are growing on each other. The layer of a surface neo-angiogenic fractal is covered by the next layer of neo-angiogenic fractal supplying the tumor layer by layer.

The Darcy-principle describes the velocity of the liquid in leakage [37]. The mathematical form from Hagen-Poiseuil and Navier-Stokes equations

$$\bar{v} = \mu \text{grad } p \quad (7)$$

where  $p$  is the pressure. In aqueous solutions like the blood, the incompressibility of the liquid is assumed, so

$$\text{div } \bar{v} = 0 \quad (8)$$

Hence the pressure satisfies the Laplace equation:

$$\Delta p = 0 \quad (9)$$

Which is completed by boundary conditions, which has a definite role in the forming of the branching pattern, but in our present mathematical process have no role.

The triggering electric field acts in porous media too, where the differential Ohm-law is effective:

$$\bar{j} = \sigma \bar{E} \quad (10)$$

where  $\bar{j}$  is the current density and  $\bar{E}$  is the electric field-strength.

Due to the relatively large conduction of the extracellular electrolyte, no space-charge could be formed. Hence

$$\text{div } \bar{j} = 0 \quad (11)$$

On the other hand, the field is induced by standing charges, so it is curl-free:

$$\bar{E} = \text{grad } \Phi \quad (12)$$

Accordingly, the formed electric potential satisfies the Laplace equation:

$$\Delta \Phi = 0 \quad (13)$$

Compared this to (9) shows the mathematical equivalency of the electric trigger of this phenomenon with the leakage problem in space.

Consequently, from the above, while the angiogenesis stops by the maturation of the healthy cell, in the case of the malignancy the neo-angiogenesis remains active until the nutrients input balances the requested amount of keeping the tumor alive. When the balance is created, no further growth happens. However, during the permanent division of tumour-cells, the electric trigger remains active, and the balance of the amount of transport and utilization cannot be created.

The nutrition influx made by transport of the vascular-network is proportional a power of the number of the cells which are alimeted, due to the self-similarity of the construction process. This power exponent appears as the fractal character of the pattern of the actually formed vascular-network.

The physical mechanism of structural developing of the cells is probably iden-

tical or very similar to the healthy and tumorous growth. The tree-branch-like structure of the leakage currents is a morphogenetic stimulus. The crucial factor is the fission of the cells. During the division, the cell isolates itself from the standard healthy network. By this isolation, its effective membrane surface growth and the mobility of ionic species (nutrients and waste) grow as well. The cells in fission have definitely smaller membrane potential than the same cell in the healthy network [23]. This relatively negative charge is essential for the start of flows of micro-currents. Furthermore, the individuality constructs a freedom of their shapes (which follows the collapse of the normal cytoskeleton during the fission), and usually, they are more globular than there are in networks. With this, the cells in fission minimize their volumetric energy and maximize their relative surfaces for metabolic transfers. During the fission process, the free extracellular electrolyte in the vicinity of the cell allows higher diffusion rates of ions and molecules and could happen more glucose supply from and more waste efflux to the neighborhood. These processes support the drastic increase in the energy demand of the division, producing two daughters.

In the case of tumor development, the cluster of the dividing cells (micro-tumour) has relative negative potential on its cluster (a tumor) surface due to the relative negativity of the surface of the cells inside the cluster. The surface of starting tumor by developing micro-cluster remains negative, which induces the development of new blood vessels. The cancerous cluster of cells has a united action to create the potential for angiogenesis; the demand for nutrients is collective, while the healthy cells are forming their optimal pattern individually. The neo-angiogenesis dominantly supplies the tumor surface. The development of the new vessels occupies the surface layer of a tumor [38]. Inside of the cluster mostly has less oxygen, and starts the fermentative ATP generation, like in healthy cases by hypoxia.

In many cases, the expected survival time of cancerous patients is approximated from the doubling-time of tumor size [7]. In the following, we use this approximation, and transform the allometric parameter from the mass [2] to the characteristic size in the scaling, using the experimentally easy measurable  $L_0$  linear size of the tumorous cell-cluster.

Similarly, to (2) the connection of the mass and its characteristic length of the transport network have scaling of fourth power, so

$$m_t = K_t l_t^4 \quad (14)$$

where  $K_t$  is constant and  $l_t$  is the characteristic (average) length of the transport network (dominantly neo-angiogenic) and  $m_t$  is the actual mass of a tumor. Due to the dense surface growth of the new vessels, we can consider its asymptotic structure by Hilbert fractal [39], having fractal dimension [40]. This means the linear size of a tumor ( $L_t$ ) is proportional with  $l_t$ , so the linear size of the tumour determines the mass by scaling:

$$m_t = K_0 L_t^4 \quad (15)$$

where  $K_0$  is a constant, which value depends on the structure and density of

the tumour. When the asymptotic mass is  $M_t$  and the asymptotic linear size of the tumour is  $L_{t0}$ , then:

$$M_t = K_0 L_{t0}^4 \quad (16)$$

moreover, consequently:

$$\left(\frac{m_t}{M_t}\right)^{\frac{1}{4}} = \frac{L_t}{L_{t0}} \quad (17)$$

From (6) we get that the geometric size of growing could be expressed as a universal expression like:

$$\begin{aligned} \frac{L_t(\tau)}{L_{t0}} &= 1 - e^{-\tau} \\ \tau &= \frac{at}{4M_t^{\frac{1}{4}}} - \ln\left(1 - \frac{L_t(\tau=0)}{L_{t0}}\right) = \frac{at}{4K_t L_{t0}} - \ln\left(1 - \frac{L_t(\tau=0)}{L_{t0}}\right) \end{aligned} \quad (18)$$

When the size of a tumor is  $L_{detec}$  in the actual time of detection, and the lethal size is approximated as  $L_{leth}$  both parameters are experimentally determined.

Assuming that the asymptotic size is longer than both the detected and lethal sizes, then the exponential function well approximated by the two first terms of its Taylor series, like:

$$\langle t \rangle := (t_{leth} - t_{detec}) = \frac{4K_t}{a} (L_{leth} - L_{detec}) \quad (19)$$

This is valid for ideal alimentation of a tumor, so here  $\langle t \rangle = \langle t \rangle_{id}$ . The formulation shows definite similarities with the formulation of survival time by approximation with diffusion theory [41].

As we had shown elsewhere, the growth of the mass of a tumor in case of non-ideal alimentation (shortage of nutrients) support is described with the formulation:

$$\frac{dm_t}{dt} = am_t^\alpha \left(1 - \left(\frac{m_t}{M_t}\right)^{1-\alpha}\right) \rightarrow \frac{d\left(\frac{m_t}{M_t}\right)^{1-\alpha}}{dt} = \frac{a(1-\alpha)}{M_t^{1-\alpha}} \left(1 - \left(\frac{m_t}{M_t}\right)^{1-\alpha}\right) \quad (20)$$

Hence its solution:

$$\begin{aligned} \left(\frac{m_t}{M_t}\right)^{1-\alpha} &= 1 - \left(1 - \left(\frac{m_{t0}}{M_t}\right)^{1-\alpha}\right) e^{-\frac{a(1-\alpha)t}{M_t^{1-\alpha}}} = 1 - e^{-\frac{a(1-\alpha)t}{M_t^{1-\alpha}} + \ln\left(1 - \left(\frac{m_{t0}}{M_t}\right)^{1-\alpha}\right)} = 1 - e^{-\tau}, \\ \tau &= \frac{a(1-\alpha)t}{M_t^{1-\alpha}} - \ln\left(1 - \left(\frac{m_{t0}}{M_t}\right)^{1-\alpha}\right) \end{aligned} \quad (21)$$

where  $\alpha$  depends on the fractal dimension of the vascular-network.

Usually, in healthy structures, the fractal dimension of the length of the transport network is 1, the effective surface in this state has fractal dimension 3,

and the volume where it fills up has dimension 4. In the tumor case, the linear fractal dimension is not valid ever more; the angiogenic structures cover the surface of a tumor densely. In measurements, the fractal dimension of the transport network in cancer is higher than 1. In the asymptotic situation, we expect complete covering with Hilbert fractal pattern with dimension 2 of the network pattern. In the case of DLA in 3-dimension is about 2.5 [42], in plane growth 1.41, [43].

Let us denote by  $\varepsilon$  the increase in transport-network dimension from 1. In this last case,

$$\alpha = \frac{3 - \varepsilon}{4 + \varepsilon} \quad (22)$$

which is in plane DLA growth case  $\varepsilon = 0.41$ , so  $\alpha = \frac{2.59}{4.41} \approx 0.587$ .

Hence:

$$\begin{aligned} \left( \frac{L_t(\tau)}{L_{t_0}} \right)^{1+\varepsilon} &= 1 - e^{-\tau} \\ \tau &= \frac{a \frac{1+\varepsilon}{4+\varepsilon} t}{M_r^{1+\varepsilon}} - \ln \left( 1 - \left( \frac{L_t(\tau=0)}{L_{t_0}} \right)^{1+\varepsilon} \right) = \frac{a \frac{1+\varepsilon}{4+\varepsilon} t}{K_r L_{t_0}^{1+\varepsilon}} - \ln \left( 1 - \left( \frac{L_t(\tau=0)}{L_{t_0}} \right)^{1+\varepsilon} \right) \end{aligned} \quad (23)$$

When the actually detected linear size of the cancer is again  $L_{detec}$  and  $L_{leth}$  is the lethal size, both have to be determined in every tumour-type on the experimental way. When the asymptotic size is considerably more than both, the average survival time in case of non-ideal alimentation in optimized support of the complete volume ( $\langle t \rangle_{nidopt}$ ) with the available nutrients:

$$\langle t \rangle_{nidopt} := (t_{leth} - t_{detec}) = \frac{K_t}{a} \frac{4 + \varepsilon}{1 + \varepsilon} (L_{leth}^{1+\varepsilon} - L_{detec}^{1+\varepsilon}) \quad (24)$$

This survival time shows the non-ideal (shortage) supply of alimentation but the available nutrients as maximal as possible [2]. In this case, the boundary conditions govern the process which does not distribute the available nutrients optimally in a complete tumour, prefers the outer layers supplied better by the neo-angiogenic formations. This calculation shows the considerable difference from the approximated average survival time by diffusion theory [41].

Another approach of non-ideal alimentation is when we assume the ideal distribution of the available nutrients in all over the volume. In this case, we have four-dimensionality of the dependence of metabolism from the mass [44]. In this case

$$\alpha = \frac{3 - \varepsilon}{4} \quad (25)$$

Hence

$$m = K L_0^{1+\varepsilon} \quad (26)$$

Moreover, consequently:

$$\langle t \rangle_{\text{nonid4}}(\varepsilon) := (t_{\text{leth}} - t_{\text{detec}}) = \frac{K_t}{a} \frac{4}{1+\varepsilon} (L^{\text{leth}+\varepsilon} - L^{\text{detec}+\varepsilon}) \quad (27)$$

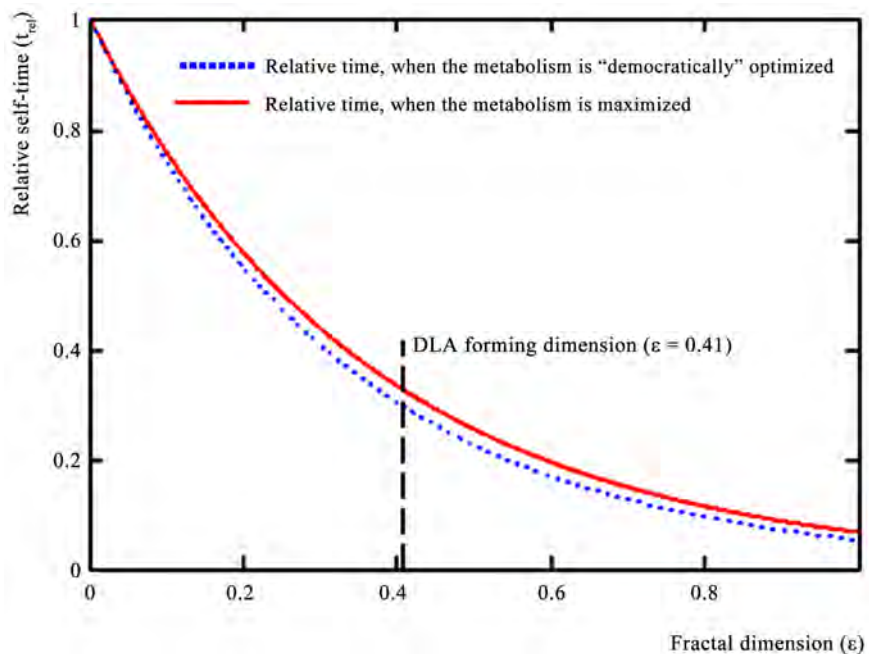
This calculation shows considerable difference again from the approximated average survival time by diffusion theory.

Comparison of survival times in healthy, ideal and cancerous, non-ideal alim-entation conditions it is evident that the survival time decreases by the grow-ing limitation of nutrients. Survival time vs. the fractal dimension, which char-acterizes the degree of non-ideal conditions, shows a rapid decline in survival by growing fractal dimension, **Figure 4**.

In the case of an optimal distribution of nutrients throughout a tumor, the decrease in survival is slightly more than in the situation of heterogeneity, which maximizes the metabolic rate of a tumor. In the case of simple DLA, forming the survival of maximized and ideal metabolic conditions is 32.5% and 29.5%, re-spectively. In the case of the complete surface covering (a blood-pool) when a Hilbert fractal is formed (most advanced cancer cases), the corresponding values are 6.9% and 5.5%.

## 6. Conclusion

The primary metabolic transport is governed by the free membrane surface of the cell. This free surface is suppressed by various connections of the cells (junc-tions and adherent connections), intended to additional material and energy transports. This precise control of cell metabolism decreases primary metabolic transport through the free surfaces of the cells. The cellular network is formed by triggering the endogenous electric fields, which are dominantly governed by cell



**Figure 4.** The relative survival time vs. fractal dimension (changing of limiting the alim-entation conditions), shows shortening of survival by the development of a tumor.

actual membrane potential. The proliferation of the cell occurs with low cell-membrane potential resulting negativity relative to its environment. Cancer-cells break their cellular connections “free” their membrane surface for intensive metabolic activity, mainly by fermentative, anaerobic way (Warburg effect [45]), and also these cells have lower membrane potential than their healthy counterparts. The malignant proliferation has certain similarities to the leakage transport of liquid in porous media, substituting the pressure with endogenous tumor potential. The average survival of the tumour-cells shortens by the growing fractal dimension of the newly built angiogenic network and modifies by the kind of alimentation of the tumour.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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# Mechanics of Twisted DNA Molecule Adsorbed on a Biological Membrane

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## Abstract

DNA is the carrier of all cellular genetic information and increasingly used in nanotechnology. The study of DNA molecule achieved *in vitro* while submitting the DNA to all chemicals agent capabilities to destabilize links hydrogen, such as pH, temperature. In fact, the DNA enveloped in the membrane cellular, so it is legitimate to study the influence of membrane undulations. In this work, we try to show that the fluctuations of the membrane can be considered as a physics agent is also capable to destabilize links hydrogen. In this investigation, we assume that each pair base formed an angle  $\alpha_n$  with the membrane's surface. We have proposed a theoretical model, and we have established a relationship between the angle formed by the pair base  $\theta_{eq}$  and angle  $\alpha_n$  formed by the membrane and each pair base. We assume that DNA and biomembrane interact via a realistic potential of Morse type. To this end, use is made of a generalized model that extends that introduced by M. Peyrard and A. R. Bishop in the past modified by M. Zoli. This generalized model is based on the resolution of a Schrödinger-like equation. The exact resolution gives the expression of the ground state, and the associated eigenvalue (energy) that equals the free energy, in the thermodynamic limit. First, we compute the denaturation temperature of DNA strands critical temperature. Second, we deduce all critical properties that mainly depend on the parameters of the model, and we quantify the effects of the membrane undulations. These undulations renormalize all physical quantities, such as harmonic stacking, melting temperature, eigenfunctions, eigenvalues and regular part of specific heat.

## Keywords

Biomembrane, DNA Molecule, Denaturation, Interactions, Critical Properties

## 1. Introduction

The Deoxyribose-Nucleic-Acid molecule (DNA) is considered among the most important biological systems for living beings. Since Watson and Crick unveiled its topological structure [1]. This molecule has become a vast field of research. All the genetic information that controls the cell reproduction is coded there, constituting the most sensitive molecule of the cellular nucleic.

A chromosome with protein components is a complete DNA molecule. Amino acids are assembling in the right order to produce the protein. This assembly is triggered by a chemical message carried by the DNA of each gene, tells the cell how to organize this assembly. Monomers that constitute the molecule of DNA are called nucleotides contained information. The structure of the DNA molecule consists of a base and a skeleton alternating phosphate ions and sugar molecules. In DNA, there are four different nucleotides, namely guanine (G), adenine (A), cytosine (C) and thymine (T), whose repeated stacks are formed by AT or GC. The stability of the double helix, *i.e.* its denaturation resistance depends on its sequence: the G-C rich sequences have a greater resistance to denaturation than the A-T rich one. Because the opening of the G-C base requires the breaking of three hydrogen bonds, while the opening of a pair of A-T involves only two hydrogen bridges. In the case of thermal denaturation, the mean denaturation temperature of a given chain is effectively related to the percentage of G-C contained in the sequence [2].

Several works have been interesting by the study of DNA-interface interactions considered as a subject of general nature. DNA interactions with surfaces can be repulsive leading to confinement or depletion [3] [4]. In this situation, there exist a repulsive interaction between negatively charged phosphates of DNA and phospholipids of membranes and contributes to enclose the genetic material within the cell [5]. The depletion forces also confine DNA within viral capsids [6]. To indicate the repulsive interactions are a common requirement in micro and nano-fluidics [7]. On the one hand, the attractive interactions lead to adsorption on a surface. The adsorption studied is done by x-ray reflectivity [8]. In some recent work [9], a theoretical analysis of such scenarios is based on the self-consistent field theory approach. In this work, they treated the importance of the charge correlation effect.

The thermodynamic magnitudes of DNA are affected by several factors, for example the thermodynamic properties with the interaction of the solvent on the nonlinear dynamical structure of a DNA segment [10], by using a time-independent perturbation approach. Also, for a short fragment of heterogeneous DNA with a stabilizing solvent interaction term, the technique used in this case is the imaginary time path integral formalism that is applied to a nonlinear Hamiltonian [11]. These nonlinearities in DNA dynamics were first emphasized by Englander *et al.* [12] who interpreted the formation of temporary open segments of base pairs as moving defects propagating coherently along the backbone of the molecule. This phenomenon has been treated like a bubble dynamics in a random DNA sequence, in a study of the localization of *denaturation* [13].

The *denaturation* transition is done by the hydrogen bond rupture between two pair bases, so the set of the two strands is transformed into a single strand. This phenomenon is done by several factors, for example, when a sufficiently heated solution of DNA. The temperature at which the DNA strands are half denatured, meaning half double-stranded, half single-stranded, is called the *melting* temperature ( $T_m$ ) or *denaturation* temperature ( $T_d$ ). The amount of strand separation, or melting, is measured by the absorbance of the DNA solution at 260 nm (absorb in the ultraviolet). Nucleic acids absorb light at this wavelength because of the electronic structure in their bases, but when two strands of DNA come together, the proximity of the bases in the two strands quenches some of this absorbance. As the DNA becomes denatured, its absorption of light ultraviolet increases, when the two strands separate, this quenching disappears, and the absorbance rises 30% - 40%. This is called Hyperchromicity. The Hypochromic effect is the effect of stacked bases in a double helix absorbing less ultra-violet light.

For a quantitative study, Thierry Dauxois and Michel Peyrard presented a model for the dynamical structure of DNA that can be considered as an extension of the usual Ising-like statistical approach to the melting curves. Also, Thierry Dauxois and Michel showed by numerical simulation method at constrained temperature show that it provides a good qualitative description of the collective motions of the base pairs, including their large-amplitude fluctuational openings and the emergence of the denaturation bubbles from the thermal fluctuation [14].

In this paper, we focus on the statistical of a DNA molecule on the fluid membrane, our aim is to determine the quantity physics. Our system physics constituted by a fluid membrane fluctuating around a horizontal, plane on this the latter adsorbed a DNA molecule. Firstly, we determine the partition function, from which we establish the free energy of the system. Based on the latter, we derive the magnitudes thermodynamics such as heat energy. As results, we have showed that the constant of harmonic stacking is renormalized, and the DNA becomes more elastic. This constant depends crucially on the membrane parameters. The thermal fluctuations of membrane modify the depth of interaction potential of staking and inverse length. On the other hand, we concluded that the fluctuations of the membrane increase the denaturation temperature. In the transition point we constant that the average separation between base-pair and specific heat are diverging.

The remaining of the presentation proceeds as follows. In Section 2, we presented the physical system with its parameters, and the Section 3 is reserved to formalism for partition function and free energy, the exact study of the denaturation transition is presented in the Section 4, Some concluding remarks are drawn in Section 5.

## 2. Description of the Physical System and the Basic Equation

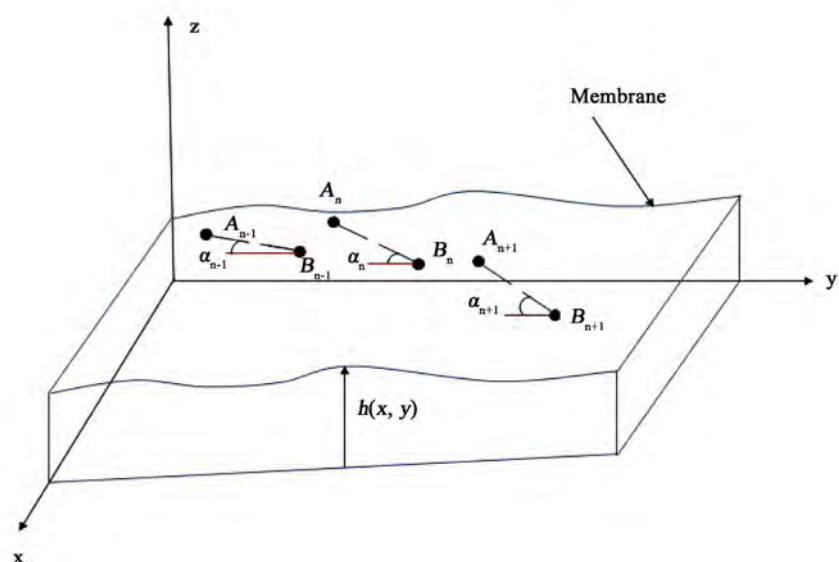
The denaturation transition can be achieved *in vitro*, while submitting the DNA

to all chemicals or physical agent capabilities to destabilize links hydrogen, such as pH, temperature, certain solvents, alkaline agents, high ionic concentrations [10], in this paper, the authors investigated the effect of solution concentrations on physical quantities such as specific heat, entropy, melting temperature, and the mean hydrogen bonding stretching.

In the living cells, the DNA molecule is compacted in a biological membrane. Quantitative understanding and optimization of its functions require precise experimental characterization and accurate modelling of DNA properties on the biological membrane. The legitimate question, how the thermal fluctuations of the membrane affect the *denaturation* temperature of the DNA molecule, and its influence on thermodynamics quantities. Due to the nature of electrically charged DNA, as well as superficially charged cell membrane leads to the phenomenon of adsorption [9]. Therefore, in this investigation, we assume a DNA-molecule adsorbed on a fluctuating membrane, such as each base pair of index  $n$ , formed an angle  $\alpha_n$ , with the plan of the membrane (see **Figure 1**). In this model, the interaction between DNA-molecule and membrane per area has an attraction, as well as hard wall repulsion for a base pair residing at a point on the membrane surface.

On the other hand, we introduce the twist angle  $\theta_{eq} = cte$ , for the pairs bases adsorbed, we take the equilibrium twist angle value, in our situation  $\theta_{eq} = \pi/10$ , we choose the model of Dauxois-Peyrard-Bishop (DPB) modified by Zoli [11]. This author introduced the rotation angle between adjacent bases  $n$ , and  $n-1$  along the DNA backbone. The twist angle between adjacent base  $n$ , and  $n-1$ , we assume constant, therefore

$$\begin{cases} \theta_{eq} = \theta_n - \theta_{n-1} \\ \theta_{eq} = \theta_{n+1} - \theta_n \end{cases} \quad (1)$$



**Figure 1.** Biological membrane with a twisted DNA adsorbed.

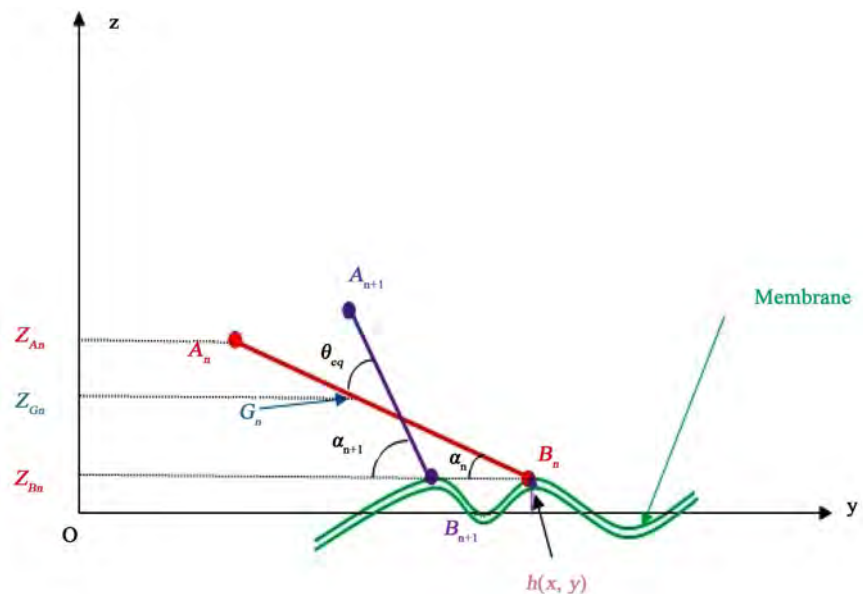
We consider the adsorption of DNA on the membrane as the adsorption of copolymer on the substrate, which forms loops, so there are a few base-pair are adsorbing on this membrane for each loop. In the other hand, some work show that [15] the distance between adjacent bases in closed case of base pair ( $\sim 3.3 \text{ \AA}$ ) is smaller than the distance of separation between base pairs ( $\sim 18 \text{ \AA}$ ), but it's clear that length between base pair in the opening state is greater than the distance between two base, so with these considerations we assume that the two bases adjacent are coplanar. We take for example the first adjacent bases (base 1 and 2), we can establish the first relation between the angles  $\alpha_1$  and  $\alpha_2$ , such as  $\alpha_2 = \theta_{eq} + \alpha_1$  and the second adjacent bases (base 2 and 3), we find  $\alpha_3 = 2\theta_{eq} + \alpha_1$ , etc. (see **Figure 2**), finally, we get the relationship between  $\theta_{eq}$  and  $\alpha_n$

$$\alpha_n = (n-1)\theta_{eq} + \alpha_1 \quad (2)$$

where  $\alpha_1$  is the first angle between adsorbed base pair and membrane, from this relationship, we can determine the maximum number of base pairs (bp) adsorbed on the membrane and contribute to the denaturation transition phenomena by the following relation:

$$n_{\max} = \frac{1}{\theta_{eq}}(\alpha_n - \alpha_1). \quad (2a)$$

As long as adsorption takes place with a few monomers (we take for example  $n_{\max} = 5$ ) to form the brush, we can choose for example  $\alpha_1 = \pi/10$ , and the number of base pair which contribute to adsorption is  $0 < n \leq 5$ , we deduct that  $0 \leq \alpha_n \leq \pi/2$ . In the absence of the membrane, the number of base pairs that contribute to the denaturation transition is of the order of 20 bp for  $N \sim 10^3$  total number of base pairs [13].



**Figure 2.** Cross-section of a membrane with an adsorbed DNA molecule.

The double-strand is denoted by the base sequence  $A_1B_1 \cdots A_nB_n$  (where  $A_k$  and  $B_k$  are the nucleotides with  $A_k, B_k \in \{A, C, G, T\}$ , of one of the strands, ordered from the 5' to 3' end. The distance between the mass center of the base pairs and a point situated on the surface of the membrane is given by barycenter technique  $z_{Gn} = z_{An} + z_n m \sin \alpha_n$ , where  $m = m_{Bn} / (m_{An} + m_{Bn})$  is the reduced mass,  $z_{An}$  is the abscissa of the nucleotide  $A_n$ , and  $z_n$  is the distance between two nucleotides  $A_n$  and  $B_n$  (i.e. is the length of the hydrogen bond), since we are interested in the bases of pairs, that is *adsorbed* on the membrane, we take  $z_{An}$  or  $z_{Bn}$  equal the fluctuation amplitude of the membrane  $h(x, y)$

## 2.1. The Hamiltonian of Membrane

The membrane is a flexible, continuous surface that has a size  $L$  and area  $S = L^2$ . Membrane local position vectors are, in the Monge representation,  $\mathbf{r} = x\hat{x} + y\hat{y} + h(x, y)\hat{z}$ , where  $h(x, y)$  is the height of the membrane. The position of the (almost flat) membrane is specified through the displacement field  $h(x, y)$ . The surface fluctuates around the horizontal plane  $z = 0$ . The equilibrium statistical mechanics of the membrane is based on the Canham-Helfrich Hamiltonian [16] [17]

$$H_m = \frac{1}{2} \int_S d^2\rho \left[ \kappa (\nabla^2 \rho h(\rho))^2 + \sigma (\nabla \rho h(\rho))^2 \right] \quad (3)$$

where  $\kappa (\approx 20 - 50 k_B T)$ , is the membrane bending rigidity,  $\sigma$  is the microscopic membrane surface tension, and  $\rho = x\hat{x} + y\hat{y}$  is the projection of  $\mathbf{r}$  in the reference plane,  $\nabla_\rho = (\partial_x, \partial_y)$  is the cartesian operator in the basic  $(x, y)$ , and  $S$  is the projected membrane area. Although we mainly refer to membranes, our development below with this Hamiltonian applies to a variety of membranes and interface including *fluid* membranes ( $\sigma = 0$ ) and *elastic* interface ( $\kappa \approx 0$ ).

## 2.2. Hamiltonian Model of DNA

In our investigation, we choose the model (DPB) modified by Zoli [11] [14], thus generalizing the DPB Hamiltonian, is given by

$$\mathcal{H}_{DNA-z} = \sum_{n=1}^N \left[ \frac{m \dot{z}_n^2}{2} + \frac{K}{2} (z_n^2 - 2z_n z_{n-1} \cos \theta_{eq} + z_{n-1}^2) + D_0 (e^{-az_n} - 1)^2 \right], \quad (4)$$

where  $m$  is the base pair reduced mass,  $\dot{z}_n = dz_n/dt$  is the nucleotide velocity,  $K$  is the harmonic stacking,  $D_0$  and  $a$  are the pair dissociation energy and the inverse length setting the hydrogen bond potential range for the  $n$ -th base pair. The first term is the kinetic energy, the second term is the potential energy of the longitudinal links and the last term represents the dissociation energy of the pair (for a very deep reading see the Ref. [14]). The settings in this Hamiltonian are adjusted to match our problem ( $K = 4 \text{ eV} \cdot \text{nm}^{-2}$ ,  $D_0 = 0.15 \text{ eV}$ ,  $a = 0.63 \text{ nm}^{-1}$ , [18]).

## 2.3. Interaction between DNA Molecule and Membrane

The DNA molecule and membrane are subject to mutual interaction which we

denote by

$$V_{DNA-m} = \sum_{n=1}^N \int d^2 \rho U(z_{Gn} - h(\rho)) \quad (5)$$

the sum of all the base pairs, and continued sum covers the surface of the membrane. The potential that can be used to model interactions such as the interaction between an atom and a surface is the Morse potential. Because of its simplicity, it is not used in modern spectroscopy [19]. However, its mathematical form has inspired the MLR (Morse/Long Range) potential, which is the most used potential energy function for spectroscopic data fitting [19]. The potential chose to mimic the adsorption potential by a simpler one, the Morse potential

$$U(z_{Gn} - h(\rho)) = \frac{U_0}{\mathcal{S}} \left[ 1 - \exp(-b_0(z_{Gn} - h(\rho))) \right]^2, \quad (5b)$$

we replace  $z_{Gn}$  by its expression in this potential we find

$$U(z_n) = \frac{U_0}{\mathcal{S}} \left[ 1 - \exp(-bz_n \sin \alpha_n) \right]^2, \quad (5c)$$

with  $b = mb_0$  and  $\mathcal{S}$  is the membrane's surface. In our model, the interaction  $U(z_n)$  between base pair and membrane per area has an attraction, as well as hard wall repulsion (impenetrability) for a base pair residing at a position  $(\rho, h(\rho))$  on the surface. Such impenetrability by DNA molecule is conceivable even in fluid membrane unless the striking barrier formed by the lipid bilayer self-assembly is disturbed by a strong attraction, (*i.e.* between hydrophobic segment in the DNA-chain and inner hydrophobic part of the bilayer) leading to chain penetration into the membrane, the choice of the Morse potential to ensure the adsorption phenomena, in a similar work [20], the potential chosen is the hard square-well with depth  $U_0$  and width  $b_0$ . The Parameters for the Morse potential are adjusted to have a good match at the minimum with the true potential ( $b_0 = 0.3 \text{ nm}^{-1}$ ,  $U_0 = 0.05 \text{ eV}$ ).

### 3. The Partition Function of System and Free Energy

For a chain containing  $N$  units (nucleotide), the classical partition function of the system may be factored as

$$\begin{aligned} \mathcal{Z} &= \int \mathcal{D}p_n \mathcal{D}h(\rho) \mathcal{D}z_n \mathcal{D}\alpha_n \exp[-\beta(\mathcal{H}_m + \mathcal{H}_{DNA} + V_{DNA-m})] \\ &= \mathcal{Z}_p \times \int \mathcal{D}h(\rho) \exp[-\beta(\mathcal{H}_m)] \times \int \mathcal{D}z_n \left\{ e^{-\beta \mathcal{H}_{DNA}} \int \mathcal{D}\alpha_n \exp[-\beta(V_{DNA-m})] \right\} \end{aligned} \quad (6)$$

where we define as usual  $\beta = 1/k_B T$ , with  $T$  the absolute temperature,  $k_B$  Boltzmann's constant. The momentums parts are readily integrated to give the familiar kinetic factor for  $N$  particles  $\mathcal{Z}_p = (2\pi m k_B T)^{N/2}$ . The sum on the variable  $\alpha_n$  in Equation (6) is independent of the other variables, so we can compute this sum separately, therefore we get the following relation (see **Appendix**) [21]

$$\begin{aligned} &\int_0^{\pi/2} \mathcal{D}\alpha_n e^{-\beta U_0 (1 - \exp(-bz_n \sin \alpha_n))^2} \\ &= \frac{1}{bz_n} \left[ \frac{1}{\sqrt{\beta U_0}} e^{-\beta U_0 (1 - e^{-bz_n})^2} \right] \times \sum_{k=0}^{\infty} \frac{2^k \left[ \sqrt{\beta U_0} (1 - e^{-bz_n}) \right]^{2k+1}}{(2k+1)!} \end{aligned} \quad (7)$$

we are restricted to the first order, and, we have been interested in the phenomenon of breathing, which is affected near of point of equilibrium, then  $z_n$  is weak. Thus, we get the potential expressed by the following relationship

$$\int_0^{\pi/2} \mathcal{D}\alpha_n \exp\left[-\beta U_0 \left(1 - \exp(-bz_n \sin \alpha_n)\right)^2\right] = \exp\left[-\beta U_0 \left(1 - e^{-bz_n}\right)^2\right] \tag{7a}$$

The partition function (6) becomes

$$\begin{aligned} \mathcal{Z} &= (2\pi m k_B T)^{N/2} \mathcal{Z}_0 \int \mathcal{D}z_n \exp\left\{-\beta \sum_{n=1}^N \left[\frac{K}{2} (z_n^2 - 2z_n z_{n-1} \cos \theta_{eq} + z_{n-1}^2)\right]\right\} \\ &\times \exp\left\{-\beta \left[D_0 \left(1 - e^{-az_n}\right)^2 + U_0 \left(1 - e^{-bz_n}\right)^2\right]\right\} \\ &= (2\pi m k_B T)^{N/2} \mathcal{Z}_0 \times \mathcal{Z}_z, \end{aligned} \tag{8}$$

where  $\mathcal{Z}_0 = \int Dh(\rho) \exp(-\beta \mathcal{H}_m)$  is the partition function of the free membrane for developing the part related to the twist angle in the last equation, we are introducing sum and difference coordinates  $d_n = (z_n + z_{n-1})/2$  and  $\delta_n = z_n - z_{n-1}$ . In this work, we also assume the twist angle is very low, which affects the harmonic part, becomes  $-\beta K (z_n - z_{n-1})^2 / 2 - \beta K \theta_{eq} z_n z_{n-1} / 2$ . Therefore  $\mathcal{Z}_n$  can be expressed in the form

$$\mathcal{Z}_z = \int \sum_{n=1}^{+\infty} dz_n e^{-\beta E_{pot}(z_n, z_{n-1})}, \tag{9}$$

where  $E_{pot}$  denotes the total potential energy in  $z_n$ . This integral can be evaluated exactly in the thermodynamic limit of a large system ( $N \rightarrow \infty$ ) using the eigenfunctions and eigenvalues of the transfer-integral operator [22] [23] [24]

$$\int dz' e^{-\beta E_{pot}(z, z')} \varphi_i(z') = e^{-\beta \epsilon_i} \varphi_i(z). \tag{10}$$

To solve this integral we change the variable of integration from  $z$  to  $z'$  (where  $z' = d + \delta$ ), in what follows, we assume  $d_n \approx z$ , and introducing  $\varphi_i(d + \delta) \approx \varphi_i(z) + \varphi'_i(z)\delta + \varphi''_i(z)\delta^2/2$ , and performing the Gaussian integrals over  $\delta$ . From this equation, with the new parameter, in the continuum limit approximation, the transfer integral eigenvalue problem can be reduced the following Schrödinger-like equation

$$\frac{d^2 \varphi_i}{dz^2} + 2\beta^2 K'(\epsilon_i - s - V_{tot}(z)) \varphi_i(z) = 0, \tag{11}$$

where the harmonic stacking  $K'$  depend on the  $\theta_{eq}$  defined by  $K' = K(1 - \theta_{eq}^2/4)$ ,  $V_{tot}(z) = (K\theta_{eq}^2/2)z^2 + D_0(e^{-az} - 1)^2 + U_0(1 - e^{-bz})^2$  is the new potential and  $s$  is the modified entropy by the presence the angle twist

$$s = s_0 + \frac{1}{2\beta} \ln\left(1 - \frac{\theta_{eq}^2}{4}\right), \tag{12}$$

with  $s_0 = (1/2\beta) \ln(\beta K/2\pi)$  is the entropy determined by *T. Dauxois et al.* [14], from this relation we can deduce that twist angle minimizes the entropy of

the DNA-molecule and the harmonic stacking. The first term is harmonic potential, we can be transformed as a Morse potential at high temperature, we find potential with *six* pertinent parameters  $(a, b, c, D_0, D'_0, U_0)$  given by the following relation

$$V_{tot}(z) = D_0(1 - e^{-az})^2 + D'_0(1 - e^{-cz})^2 + U_0(1 - e^{-bz})^2, \quad (13)$$

where  $D'_0 = \theta_{eq}^2/2$  is the depth also, and  $c = \sqrt{K\beta}$ , this parameter is homogeneous to the inverse of a length. For a temperature  $T = 320$  K, we can estimate the values of the depth, and the range respectively,  $D'_0 \approx 5.03 \times 10^{-3}$  eV and  $c \approx 0.12$  nm<sup>-1</sup>. This potential is plotted in **Figure 3**, this potential reflects standard expression for chemical bonds and, moreover, it has the appropriate qualitative shape: 1) it includes a strong repulsive part for  $z < 0$  corresponding to the steric hindrance 2) it has a minimum at the equilibrium position  $z = 0$ , 3) it becomes flat for large  $z$ , giving a force between the bases that tends to vanish, as expected when the bases are very far apart, this feature allows a complete dissociation of the base pair, which would be forbidden if we had chosen a simple harmonic potential.

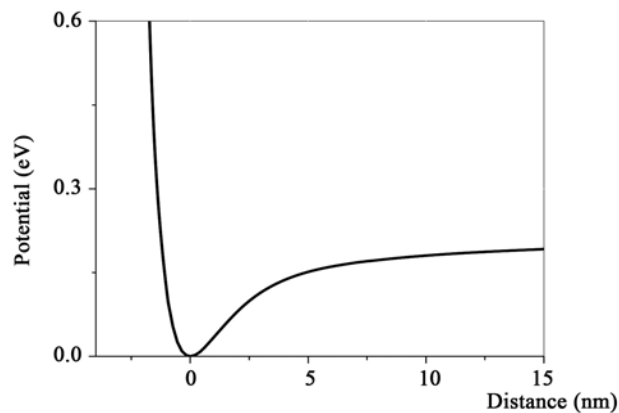
The shape of this potential is more adapted to our problem because it ensures the phenomenon of *breathing* of the DNA-molecule near its minimum has a harmonic form. So, this potential can be well fitted to the Morse potential, we can be rewritten as follows

$$V_{tot}(z) = D(1 - \exp(-\alpha z))^2. \quad (14)$$

Using the relation (13), to find the zero and minimum of this potential ( $V_{tot}(z_0) = 0$ ), then we can find the expression of the depth and the minimum ( $dV_{tot}(z_m)/dz = 0$ ). All the parameters depend on the *six* pertinent parameters, we find

$$D = D_0 + D'_0 + U_0, \quad (15)$$

is the depth of the Morse potential, and  $\alpha$  defines the range parameter given by



**Figure 3.** Reduced Morse potential, versus distance, with the ranges parameters, are  $c = 0.12$  nm<sup>-1</sup>, and the depths  $D_0 = 0.15$  eV,  $D'_0 = 5 \times 10^{-3}$  eV,  $U_0 = 5 \times 10^{-2}$  eV.

$$\alpha = a \sqrt{\frac{1 + \left(\frac{b}{a}\right)^2 \frac{U_0}{D_0} + \left(\frac{b}{a}\right)^2 \frac{D'_0}{D_0}}{1 + \frac{1}{D_0}(U_0 + D'_0)}}, \quad (15b)$$

according to the values of the parameters, we notice that this last parameter is lower than  $a$ , so the width of the potential decreases. On the other hand, the dissociation energy of the pair  $D$  (the depth of potential) increases. Note this potential describes not only the hydrogen bonds and the repulsive interactions of phosphate groups in DNA but all interactions in the system [14]. Let comment on this form of potential: the value  $z = 0$  corresponds to a closed base pair as in the Ising model, but now  $z$  can increase continuously to infinity if the two bases separate completely as in DNA denaturation. The variable  $z$  can even take negative values, corresponding to a compression of the bond linking the bases with respect to its equilibrium length. Large negative values will be forbidden by steric hindrance, which is introduced in the model by the potential linking the bases in a pair [15].

Now we determine the free energy. The calculation is similar to the one performed by Krumhansl and Schrieffer [23] for the statistical mechanics of the  $\phi^4$  field. It yields  $\mathcal{Z}_z = \exp(-N\beta\epsilon_0)$  where  $\epsilon_0$  is the lowest eigenvalue of the operator. Therefore, we can then compute the free energy of our model as the sum of the different contribution in  $\mathcal{Z}$ ,

$$\mathcal{F} = -k_B T \ln \mathcal{Z} = \mathcal{F}_0 - \frac{Nk_B T}{2} \ln(2\pi m k_B T) + N\epsilon_0, \quad (16)$$

where  $\mathcal{F}_0 = -k_B T \ln Z_0$ , is the free energy of the free membrane, with,  $Z_0 = q(2\pi k_B T)^{1/2} (\kappa q^4 + \sigma q^2)^{-1/2}$ .

The following step is to determine  $\epsilon_0$ . The presence of the membrane and thermal fluctuations affects the eigenfunctions and eigenvalues of DNA molecules, so,  $\epsilon_0 = \epsilon_0(h)$  and  $\varphi_0 = \varphi_0(r, h)$ . [20] The ground state energy  $\epsilon_0$ , as is well-known in quantum mechanics, is alternatively obtained by a variational method, by varying a variational function  $\varphi_0(r, h(\rho))$ ,  $\epsilon_0$  is given the following relation

$$\epsilon_0 = \min \left[ \int d^3 r \varphi_0(\mathbf{r}, h) \mathcal{O} \varphi_0(\mathbf{r}, h) \right]. \quad (17)$$

Since we have interested, by the distance of separation of the base pair of the DNA molecule, one stands in space united dimensional, to facilitate our development further, we use the relation [20]

$$\varphi(\mathbf{r}, h) = \frac{1}{L} \varphi(z - h(\rho)), \quad (18)$$

where  $\varphi(z)$  is the ground state variational function of the 1D free energy operator,

$$\mathcal{O}(z) = \frac{1}{2K'\beta} \frac{d^2}{dz^2} - \beta V'_{tot}(z). \quad (19)$$

where  $V'_{tot}(z) = D[e^{-2\alpha z_n} - 2e^{-\alpha z_n}] - (\epsilon_i - s - D)$ . With necessary ingredients, the expression of the minimum free energy  $\epsilon_0$  can be written as follows

$$\epsilon_m = \min \left[ \frac{1}{S} \int d^2 \rho (\nabla_{\rho} h(\rho))^2 \langle K \rangle_{\varphi_0} + \epsilon_0 \right], \quad (20)$$

where the pure DNA-molecule contribution is

$$\epsilon_0 = \langle K \rangle_{\varphi_0} + \beta \langle V'_{tot}(z) \rangle_{\varphi_0}, \quad (21a)$$

With

$$\langle K \rangle_{\varphi_0} = \frac{1}{2K\beta} \int_0^{+\infty} dz \varphi_0(z) \frac{d^2 \varphi_0(z)}{dz^2}, \quad (21b)$$

$$\beta \langle W(z) \rangle_{\varphi_0} = -\frac{1}{2} \int_0^{+\infty} dz \varphi_0(z) V \varphi_0(z). \quad (21c)$$

By a Fourier transformation for  $h(\rho) = L^{-1} \sum_q h(q) \exp(iq \cdot \rho)$  one can reduce the partition function to another form

$$\begin{aligned} \mathcal{Z} &= (2\pi m k_B T)^{N/2} \times e^{-N\epsilon_0} \mathcal{D}h(\mathbf{q}) \exp \left[ -\frac{\beta}{2q} (\kappa q^4 + \tilde{\sigma} q^2) |h(\mathbf{q})|^2 \right] \\ &= (2\pi m k_B T)^{N/2} \times \exp(-N\epsilon_0) q (2\pi k_B T)^{1/2} (\kappa q^4 + \tilde{\sigma} q^2)^{-1/2}, \end{aligned} \quad (22)$$

Here

$$\tilde{\sigma} = \sigma + \frac{N}{2S\beta} \langle K \rangle_{\varphi_0}, \quad (23)$$

is the renormalized surface tension at the state  $\varphi = \varphi_0$  corresponding to the minimum of  $\epsilon_0(h)$ , given by the Equation (20). From the partition function, we obtain the total free energy base per pair induced by its interaction with membrane

$$\frac{\beta \Delta F}{N} = f_0 = \min(f), \quad (24)$$

where

$$\frac{f}{N} = -k_B T \ln \mathcal{Z} + k_B T \ln \mathcal{Z}_0 \quad (25a)$$

With

$$\mathcal{Z}_0 = \text{Tr} e^{-\beta \mathcal{H}_m} = \sum_q (2\pi k_B T)^{1/2} (\kappa q^4 + \sigma q^2)^{-1/2}, \quad (25b)$$

is the partition function of the nude membrane. Thus, we have the following expression of the free energy

$$\frac{f}{N k_B T} = \frac{1}{2N_q} \ln \left[ \frac{(\kappa q^4 + \tilde{\sigma} q^2)}{\kappa q^4 + \sigma q^2} \right] - \frac{1}{2} \ln(2m k_B T) + \epsilon_0, \quad (26)$$

where the first term is the membrane contribution. The condition that  $f$  is the minimum for  $\varphi = \varphi_0$  leads to the new following Schrödinger-like equation

$$-\frac{1}{2K_{R\text{eff}}\beta^2} \frac{d^2\varphi_0}{dz^2} + D[e^{-2\alpha z} - 2e^{-\alpha z}] \varphi_0 = (\epsilon_0 - s - D)\varphi_0, \quad (27)$$

this equation for  $\varphi_0$  minimizing  $\epsilon_0(h)$ , Equation (21), where  $K_R$  is the re-normalized spring constant given by

$$\frac{1}{K_R} = \frac{1}{K'} \left( 1 + \frac{1}{2S_q} \frac{q^2 k_B T}{\kappa q^4 + \tilde{\sigma} q^2} \right), \quad (28)$$

it is easy to find

$$K_R = K'(1 + \tau)^{-1}. \quad (28a)$$

where  $\tau$  is given by the following equation

$$\tau = \frac{k_B T}{16\pi\kappa} \ln \left[ \frac{\kappa(\pi/l)^4 + \tilde{\sigma}(\pi/l)^2}{\kappa(\pi/L)^4 + \tilde{\sigma}(\pi/L)^2} \right] < 1, \quad (28b)$$

here  $l$  and  $L$  are the microscopic and macroscopic lengths that define the upper and lower wave number cutoffs. From the relationship (28a) we conclude that there is a supplementary force added to its previous  $\mathbf{f} = \mathbf{f}_0 + \Delta\mathbf{f}$  such as  $\mathbf{f} = K_R(z_n - z_{n-1})\mathbf{n}$ ,  $\mathbf{f}_0 = K'(z_n - z_{n-1})\mathbf{n}$  and  $\Delta\mathbf{f} = -\tau K'(z_n - z_{n-1})\mathbf{n}$ , ( $\mathbf{n}$  unit vector), the sign (-) signifies that this force is the inverse of the longitudinal force. These later have two different effects, one pulling the nucleotide, and the other returning it to its balanced position (similar to the nucleotide in each strand a mass attached by two springs). One deduces that the undulation of the membrane, decreases the elasticity constant  $K$ , so every strand in the double helix becomes more elastic.

## 4. Exact Study of Denaturation Transition

### 4.1. Eigenvalue and Ground State

Equation (27) is formally identical to the Schrödinger equation for a particle in a Morse potential so that it can be solved exactly [25]. So, the melting temperature of DNA adsorbed on a fluctuating membrane is given by

$$T_d = T_d^0(1 + \eta), \quad (29)$$

where  $T_d^0 = 2\sqrt{2KD_0}/ak_B$  is the denaturation temperature in the absence of membrane [14], and the quantity  $\eta$  is given by the following equation:

$$\eta = -\frac{\tau}{2} - \frac{\theta_{eq}^2}{8} + \frac{\theta_{eq}^2}{16}\tau + \frac{D'_0 + U_0}{2D_0} \left( 1 - \frac{\theta_{eq}^2}{8} + \frac{\theta_{eq}^2}{16}\tau - \frac{\tau}{2} \right) + \frac{U_0}{2D_0} \left( 1 - \frac{b^2}{a^2} \right) + \frac{D'_0}{2D_0} \left( 1 - \frac{c^2}{a^2} \right) + \left( \frac{bU_0}{2aD_0} \right)^2 + \frac{D'_0 U_0}{(2aD_0)^2} (b^2 + c^2) - \left( \frac{cU_0}{2aD_0} \right)^2. \quad (29a)$$

According to the values of the parameters  $\eta = 0.30871$ , it is deduced that the presence of the membrane increases the denaturation temperature of the DNA molecule. Also, this temperature depends on all the parameters of the problem.

Let's comment this result: like a set of external factors, the presence of the cell

membrane leads to a change in the *melting* temperature of DNA, the presence of the membrane fluctuations increasing the *melting* temperature *denaturation* temperature. According to the parameters, this temperature increases by ~30%. Therefore, when the temperature increasing, the fluctuations of membrane increasing also, which implies that the membrane undergoes a phase transition from a *flat* phase to a *crumpled* phase, *i.e.* its orientations in different points of the membrane are *decorrelated*, where the *persistence length*

$\xi_p \approx l \exp(4\pi\kappa/3k_\beta T)$ , is above the linear size  $L$ , [26]. A very recent work [27], show a good agreement between experience and numeric study, that the temperature change affects the DNA twist, and suggest that the untwisting of DNA with temperature is predominantly due to changes in DNA structure for defined backbone substates.

The eigenfunction of this system is given by

$$\varphi_0(z) = \tilde{A}_0 (2\delta)^{\delta-1/2} e^{-\alpha(\delta-1/2)z - \delta e^{-\alpha z}}, \tag{30}$$

where  $\delta = (\beta/\alpha)\sqrt{2DK_{eff}}$ , and  $\tilde{A}_0 = 1/\sqrt{\Gamma(2\delta)}$  it is the normalization constant, this equation can be rewritten according to the wave function of the DNA in the absence of the membrane we obtain

$$\varphi_0(z) = \phi_0(z)F(z), \tag{30a}$$

where  $\phi_0(z) = A_0 (2\delta_0)^{\delta_0-1/2} e^{-\alpha(\delta_0-1/2)z - \delta_0 e^{-\alpha z}}$  is the eigenfunction of DNA with  $A_0 = 1/\sqrt{\Gamma(2\delta_0)}$ , and  $F(z)$  is the function given by the following relation

$$F(z) = \sqrt{1+\eta} \exp\left[\delta_0\eta - (\delta_0\eta - az\delta_0\mu - az\delta_0\eta\mu)e^{-\alpha z}\right] \times \exp\left[-az\left(\delta_0\mu - \frac{\mu}{2} + \delta_0\eta + \delta_0\eta\mu\right)\right], \tag{30b}$$

with  $\delta_0 = (\beta/a)\sqrt{2D_0K}$ , is a constant for a free DNA, and  $\mu$ , is given by

$$\mu = \frac{U_0}{2D_0} \left(\frac{b^2}{a^2} - 1\right) + \frac{D'_0}{2D_0} \left(\frac{c^2}{a^2} - 1\right) - \left(\frac{bU_0}{2aD_0}\right)^2 - \frac{D'_0U_0}{(2aD_0)^2} (b^2 + c^2) - \left(\frac{cD'_0}{2aD_0}\right)^2. \tag{30c}$$

We notice the eigenfunction is *amplified*, by a factor  $F(z) \sim \sqrt{1+\eta}$ . The eigenvalue of the associated ground state

$$\epsilon_0 = \epsilon'_0 + \Delta\epsilon_0, \tag{31}$$

where  $\epsilon'_0$ , it is the eigenvalue of free DNA given by

$$\epsilon'_0 = \frac{a}{\beta} \sqrt{\frac{2D_0}{K}} - \frac{a^2}{2\beta^2 K} + \frac{1}{2\beta} \ln\left(\frac{\beta K}{2\pi}\right), \tag{31a}$$

and  $\Delta\epsilon_0$ , is the excess energy of ground state its expression is

$$\Delta\epsilon_0 = \left(D_0 - \frac{T_d^0 k_B}{2}\right) \left(\frac{T}{T_d^0}\right) + \left[D_0 - U_0 - D'_0 + U_0 \left(\frac{b}{a}\right)^2 + D'_0 \left(\frac{c}{a}\right)^2\right] \left(\frac{T}{T_d^0}\right)^2 \tag{31b}$$

It is noted that the thermal fluctuations of the membrane disturb the eigenvalue

lue of the DNA molecule, as well as the associated wave function. According to the values of the parameters included in Equation (31a), the difference  $\Delta\epsilon_0$ , is very low, so the energy specter of  $\epsilon_0$ , stay near to that  $\epsilon'_0$ , we conclude that membrane undulations cause a small perturbation of molecule DNA

## 4.2. Thermodynamic Magnitudes at the Critical Point

### 4.2.1. Eigenvalue and Ground State

We are recalled that to study of the *denaturation* transition of the DNA molecule, the important quantity which gives a measure of the extent of denaturation of the molecule is the mean stretching of the hydrogen bonds, which given by

$$\langle z \rangle = \int \varphi_0(z)^2 z dz, \quad (32)$$

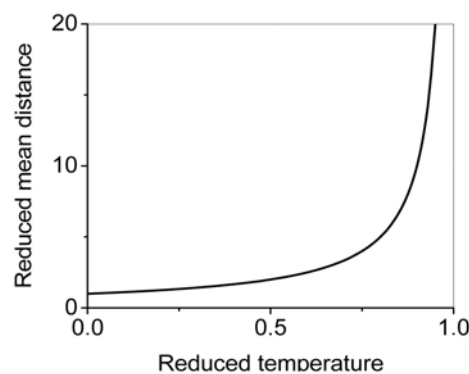
We take the results obtained in the case of unbinding transition from two interacting manifolds (strings or bilayer membranes), we find that near the transition temperature (is the similar case) [28], this average distance scale exactly as follows

$$\langle z \rangle = \frac{1}{\alpha} \left( \frac{T_d - T}{T_d} \right)^{-1}, \quad T \rightarrow T_d. \quad (33)$$

This average distance is plotted in **Figure 4**. One notices that the pace of the curve coincides with the one to find by the continuum approximation and the exact numerical calculation [14]. All methods show a divergence of the mean distance at  $T = T_d$ , corresponding to the stretch of links hydrogens, from a given temperature. We concluded that, for the weak values of  $\langle z \rangle$ , the DNA-molecules are closed and opened for the strong values.

### 4.2.2. Surface Tension and Specific Heat

A quantity that reflects the ability of the molecule of DNA adsorbed on a fluctuating membrane to accumulate energy in thermal form, it is the specific heat. Before calculating the specific heat, we attempt to determine the expression of  $\Delta\sigma$ . We consider below critical behaviors near  $T_d$ . In terms of small reduced temperature  $t = (T_d - T)/T_d > 0$ , we have all ingredients to find the expression of the surface tension depending on the temperature difference



**Figure 4.** Variation of the reduced mean distance  $\langle z \rangle$  versus reduced temperature.

$$\tilde{\sigma} = \sigma + \Delta\sigma, \tag{34a}$$

where

$$\Delta\sigma \sim \frac{N\alpha^2}{8SK_R\beta^2e} \left( \frac{T_d - T}{T_d} \right) \tag{34b}$$

this expression is according to the difference in the temperature. A simple dimensional analysis shows that  $[\Delta\sigma] = j \cdot L^{-2}$ . It is necessary to note that  $\Delta\sigma = 0$  at  $T = T_d$ .

From the relationship (26) we can derive the specific heat

$$C_v = -T \frac{\partial^2 \mathcal{F}}{\partial T^2}, \tag{35}$$

This specific heat includes a regular part, which is continuous at a transition point, and a singular part, which behaves as a power law with an exponent.

$$C_v = C_v^{si}(T) + C_v^{reg}(T), \tag{35a}$$

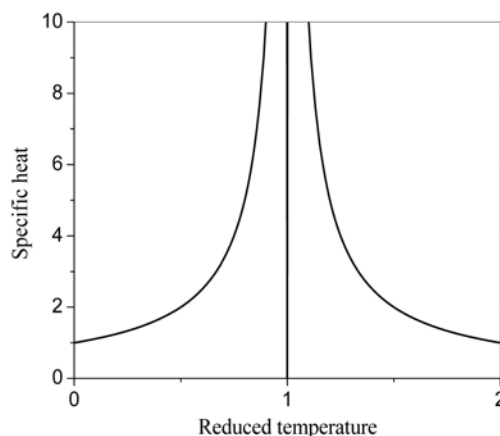
with regular part given by

$$C_v^{reg}(T) = N \frac{T}{T_d^0} \left[ D_0 - U_0 - D'_0 + U_0 \left( \frac{b}{a} \right)^2 + D'_0 \left( \frac{c}{a} \right)^2 \right]. \tag{35b}$$

Our objective is to study the critical comportment of the specific heat at denaturation temperature (singular part), therefore we get the following expression

$$C_v \sim C_v^{si}(T) \sim \left| \frac{T_d^0 - T}{T_d^0} \right|^{-\alpha}, \tag{36}$$

with a factor, where  $\alpha = 1$ , is a critical exponent. Our system is immersed in three-dimensional space ( $d = 3$ ), but the study of the spherical model has explicitly showed the role of the space dimension on critical phenomena. This model allows calculating exactly the critical properties for an arbitrary space dimension. In this case  $\alpha = (4 - d)/(d - 2)$ , (in spherical model  $2 < d < 4$ ), since  $d = 3$  we have  $\alpha = 1$ , it is a universal critical exponent, the specific heat plotted in **Figure 5**.



**Figure 5.** The variation of the specific heat  $C_v$ , versus reduced temperature.

## 5. Conclusions and Remarks

In this work, we have studied the influence of the thermal fluctuations membrane on the properties thermodynamics of DNA molecule adsorbed on the fluid membrane. We formulated the problem in terms of a mesoscopic-level partition function and free energy, using the approach variational method, which re-normalizes the elasticity constant of DNA. The undulations of the membrane, decrease the elasticity constant  $K$ . We deduce that nucleotides in each strand vibrate in the longitudinal direction. We can deduce that the modes of vibration also change. This is because the force induced by the membrane, tends to bring the nucleotide back to the equilibrium position.

Consequently, the Schrödinger-like equation which describes the state of the DNA molecule in the absence of the membrane becomes a function of the parameters of our problem. This equation is solved exactly. The resolution of this equation gives the bound state and the associated wave function. From the Schrödinger-like equation, we have determined the *melting* temperature. This latter depends also on all problem parameters. We have used the eigenfunction associated the ground state to compute the average separation  $\langle z \rangle$  between base pairs. This quantity diverges when  $T \rightarrow T_d$ . Another physical quantity has been changed by the adsorption of DNA on the membrane; it is the surface tension  $\tilde{\sigma} = \sigma + \Delta\sigma$ , where  $\Delta\sigma$  vanishes in the vicinity of the denaturation temperature  $T_d$ . In this investigation, we have also found that the heat specific diverges at melting temperature with universal exponent  $\alpha = 1$ .

For the implementation of the denaturation transition of the DNA molecule adsorbed on a membrane, the experimental results concerning the absorption of ultraviolet (UV) by a pure membrane poly (acrylic) acid (PAA) doped with graphite [29], these authors determine the absorbance as a function of the wavelength. They ascended that the absorbance increases with the increase of the concentration of graphite (in the absence of graphite there is a weak absorption [29]). For our case it is necessary to use a pure membrane (absence of graphite and DNA) and UV with a fixed wavelength at 260 nm, and then determine the maximum absorbance for different temperature values, and then use a molecule of DNA adsorbed on a membrane (experiments have been performed on artificial DNAs, which are homopolymers, *i.e.* have only one type of base pairs [15]), and then measure the absorbance for each temperature value, in the case where the absorbent is maximizing for a certain temperature, that is called the *melting* or *denaturation* temperature. It should be noted that as the DNA becomes denatured, its ultraviolet light absorption increases.

The relation (28a) raises interesting questions is the influence of the membrane on the property's DNA, especially the force-extension curve of a single DNA molecule. The first experience obtained in 1992 [30] and repeated with taller precision by several groups a few years ago [31] [32], can be repeated once again for different molecules of DNA with different values of the stiffness constant  $K$ , and look at the *melting hysteresis* comportment.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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## Appendix

In this appendix, we will try to develop the expression of following integral

$$I = \sum_{n=1}^N \int_0^{\pi/2} d\alpha_n \exp\left[-\beta U_0 (1 - \exp(-bz_n \sin \alpha_n))^2\right]. \quad (\text{A1})$$

To develop this integral we make the first variable change  $u_n = \exp(-az_n \sin \alpha_n)$ , we find

$$I = -\sum_{n=1}^N \int_1^{e^{-az_n}} du_n \frac{1}{az_n} \frac{\exp(-\beta U_0 (1 - u_n)^2)}{u_n \sqrt{1 - \left(\frac{\ln u_n}{az_n}\right)^2}}, \quad (\text{A2})$$

we use also the second variable change as follow  $t_n = 1 - u_n$ , we see that  $t_n \ll 1$ , so the integral becomes [21]

$$\begin{aligned} I &\approx \sum_{n=1}^N \frac{1}{az_n} \int_0^{1-e^{-az_n}} dt_n \exp(-\beta U_0 t_n^2) \\ &\approx \frac{1}{bz_n} \left[ \frac{1}{\sqrt{\beta U_0}} e^{-\beta U_0 (1-e^{-bz_n})^2} \right] \times \sum_{k=0}^{\infty} \frac{2^k \left[ \sqrt{\beta U_0} (1-e^{-bz_n}) \right]^{2k+1}}{(2k+1)!}. \end{aligned} \quad (\text{A3})$$

We are restricting to the first order  $k = 0$ , we find a simple development of our integral

$$I \approx \exp - \beta U_0 \sum_n (1 - e^{-az_n}). \quad (\text{A4})$$

The term  $-\beta U_0 \sum_n (1 - e^{-az_n})$ , is as similar as Morse potential.

## Parameters and Nomenclature

$\theta_{eq}$ : Twist angle between each base pair.

$\alpha_n$ : Angle formed between each base pair and membrane.

$n_{\max}$ : The maximal number of monomers adsorbed on the membrane.

$z_{G_n}$ : The abscissa of the mass center of point  $G_n$ .

$z_m$ : The abscissa of nucleotide ( $i = A_n, B_n$ ).

$m_i$ : Mass of nucleotide ( $i = A_n, B_n$ ).

$m$ : The reduced mass.

$h(x, y)$ : Fluctuation amplitude of the membrane.

$r$ : Vector position.

$\rho$ : Projection of  $r$  in the reference plane.

$\kappa$ : Membrane bending rigidity.

$\sigma$ : Microscopic membrane surface tension.

$K$ : Harmonic stacking.

$D_0$ : Dissociation energy.

$a$ : Inverse length.

$U_0$ : Dissociation energy (DNA-membrane).

$b_0$ : Inverse length.

$s$ : Entropy.

$\mathcal{Z}$  : Partition function of system.

$\mathcal{F}$  : Free energy.

$\mathcal{F}_0$  : Free energy of the free membrane.

$T_d$  : Denaturation temperature.

$T_d^0$  : Denaturation temperature in the absence of membrane.

$\varphi_0(z)$  : Eigenfunction.

$\epsilon_0$  : Eigenvalue of the associated ground state.

$\langle z \rangle$  : Mean stretching of the hydrogen bonds.

$C_v$  : Specific heat.

# Biological Stress as a Principle of Nature: A Review of Literature

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## Abstract

This review paper attempts to approximate the concept of biological stress to the stress concept in Physics using the phenomenological view of physics to discuss the source of generator forces of biological stress state. Based on the literature, parallels are drawn between the two concepts and a discussion on the steady state in open systems and homeostatic state in biological systems is developed. Using the concepts of thermodynamic entropy and informational entropy, and comparing stress in living systems and nonliving, we attempt to build a basis for a view of stress as a principle of nature linked to the adaptability property of matter, opposing entropy. It is known that the increasing number of microstates possible in a complex system increases the entropy. In that way, entropy is related to the amount of additional information needed to specify the exact physical state of a system, given its macroscopic specification. By controlling the metabolic processes (catabolism-anabolism) to decrease the entropy, stress reduces the number of possible states for which the living system could evolve, avoiding the loss of “life information”, preserving its characteristics and preventing its extinction. The loss of function of a species within an ecosystem or of cells within an organ can be showing that the limits of the stress principle were “transgressed”. That is, the intensity and/or duration of stress exceeded the capacity of living organism to process of information extracted from stressor and reprogram its physiological mechanisms, activating its adaptability process, while its internal balance is preserved.

## Keywords

Stress Concept, Biological Stress, Thermodynamic Entropy, Information Entropy, State of Stress

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## 1. Introduction

For many people, Physics and Biology are different worlds, because each one has its own language and concepts. However, in recent decades, scientific and technological advances have created overlaps between these sciences, starting the *life modeling age*. According Chao *et al.* [1], you can open the door to the creation of *virtual human reality*, *developing the ability to associate physiology and engineering knowledge with computer science*.

Indeed, details of human physiology inaccessible to experimental studies have been enlightened by means of computational simulations using physical-mathematical models of physiological systems [2]-[16]. As a starting point, the modeling and simulation in Biology require analysis and representations of its phenomena from different points of view.

Physics knowledge has been applied to study mechanical and hemodynamic of effects of stress on the musculoskeletal and circulatory systems [17]-[22]. Computer simulations have been used to verify the distribution of stress forces in blood vessel to find the structural determinants for atheromatous plaque vulnerability [23] [24]. The evolution of these plaque has been studied using growth kinetic models based on oxidized LDL (low-density lipoprotein) accumulation and mass conservation concept [25] [26], and including the endothelial permeability dependence of stress forces and other parameters [27]. Physical and mathematical modeling and computational simulation have also been applied to investigate the mechanisms underlying neurovascular coupling involving nitric oxide [28] [29].

In addition, forces involved in various types of cell motility have been modeled. The mobility of cytoskeletal filaments (stretching fast polymerization/depolymerization) and the influence of their length on the mechanical response have been investigated, using cellular force-generation models. The thermodynamic driving force for force-generation in these processes has been investigated, and the elastic-Brownian ratchet model for force generation seems valid to study the monomer addition to free cytoskeletal filament ends [30] [31] [32].

Despite the several studies and the physical-biological modeling in the description of phenomena involving stress forces acting in physiological and pathological processes [33] [34], biologic stress continues to be the subject of great controversy, from its definition to its pathophysiological inferences. Sometimes the word stress is used to denote a complex response developed by a stimulus. However, at other times, stress is mistakenly assumed to be a stimulus capable of causing illness or is used as a synonym for “illness”. In addition, alarm reactions are often called stress, despite the existence of well-established criteria to differentiate them. It is also not uncommon to hear someone confusing anxiety with stress, forgetting that in the state of stress a set of specific systemic response occurs evoked by exposure to the stressor stimulus. This full set is not present in anxiety, but usually anxiety is present in stress states [35] [36] [37] [38].

The aim of this review is to approximate the concept of biological stress to the stress concept in Physics, not through mathematical modeling, but using the phenomenological view of physics to discuss the source of generator force of biological stress state. Based on the literature, parallels are drawn between the two concepts, and a discussion on entropy, steady state in open systems and homeostatic state in biological systems is developed.

## 2. Concepts and Definitions of Stress

In strict sense, the **word stress** means “*pressure*” or “*tension*” and be stressed means “*be under pressure*” or “*be under the action of an insistent stimulus*” [38] [39]. The concept of stress was introduced in the theory of elasticity by theoretical physicist **Augustin-Louis Cauchy** in the second decade of the 19<sup>th</sup> century, based on conception of material continuity. According to the **Cauchy’s stress principle**, when a continuous body is submitted to the action of external forces, internal reactions arise throughout the body, acting between material points [40]. Thus, in Physics, the word stress refers to a measure of the intensity of the total internal force acting within a body across imaginary internal surfaces [40] [41]. Therefore, stress means the “reaction” of the body to the action of external forces, which represent the **stressor** [38] [39] [42].

In biology, the **stressor** is any stimulus or event capable of establishing the state of stress. Stress is a reactive process to reduce the negative effects caused by the stressor, and **stress of state** is a **state of resistance** that aims to maintain the internal equilibrium of the body (and mind), whose final purpose is to adapt the individual to the stressor [39] [43] [44].

Therefore, in Biology, the term stress also means “reaction”. It is not an instantaneous and localized reaction, but a reactive process that triggers a typical set of organic and behavioral responses, which has as central pattern the hyperfunction of the supra-renal gland and the increased release of **glucocorticoids (GC)**, especially cortisol in humans [45].

### 2.1. Stress in Material Body

The stress ( $\sigma$ ) is the measurement of the average intensity of all forces acting per area unit of a body submitted to a stressor stimulus, and can be represented by the equation:

$$\sigma = \frac{F}{A} \quad (1)$$

where  $F$  is the force acting over area  $A$ , and the unit of pressure in the SI is normally used for stress. In that way, stress has the meaning of pressure on the surface  $A$ , and Equation (1) is valid when the action of stressor is considered uniformly distributed over a transversal section of the material body. However, in general, it is not truth, and consequently stress at a point on a given area is different from the average stress over the entire cross section. In that case, stress can be defined at a specific point in body [40] [46].

Cauchy demonstrated that a second order cartesian tensor (Cauchy's stress tensor) was able to completely define the **state of stress** at any point in a body. A tensor is a form of representation associated with a set of algebraic operations such as the sum and the product, related to a vector space. The linear stress ( $\sigma_{ij}$ ), which represents unidimensional stress, is a tensorial entity and can be represented by a  $3 \times 3$  matrix. Using this matrix, it is possible to formulate that the force vector (or traction vector) acting on an surface element is given by

$$F = \sum_j^3 \sigma_{ij} n_j \quad (2)$$

where  $n_j$  denotes the unit vector normal to the surface element. The **Cauchy's stress tensor** ( $\sigma_{ij}$ ) is used for the stress analysis of material bodies experiencing small deformations, being other measures of stress used for large deformations [40].

Here, it is important to pay attention to fact that the deformations result from the "struggle waged" between stressor and stress, and represent the victory of the stress forces over forces contrary to the cohesion responsible for the "existence" of the material body. Deformations are inherent changes in the adaptation process, which is established to preserve the body components that, even in a new configuration, still remain in cohesion.

In Physics, stress cannot be directly measured, but is usually estimated from strain measurements and elastic properties of the material, since the *stress tensor is associated with the strain required for the body adapts to the stressor and keep its internal equilibrium*. In equilibrium, the components of the stress tensor at each point of the body satisfy the equilibrium equations, *i.e.*,  $\sigma_{ij,i} + F_i = 0$ . In addition, in equilibrium, the summation of moments on an arbitrary point is zero, indicating that the tensor is symmetric ( $\sigma_{ij} = \sigma_{ji}$ ) [40] [46].

## 2.2. Definitions of Stress in Living Systems

All organs and living tissues have their own mechanisms to keep its internal balance, *i.e.*, our body has the homeostatic property. Homeostasis is an ability of the open systems (that interact directly with its environment), especially living organisms, to regulate its internal environment in order to maintain a stable state. This is achieved by means of multiple mechanisms appropriate to promote dynamic equilibrium adjustments.

In the animal body, the dynamic equilibrium or dynamic homeostasis is characterized by a constant regulation of biophysical variables (blood pressure, temperature, salinity, acidity), nutrient concentrations (glucose, various ions, oxygen) and waste, as carbon dioxide, urea etc. [47] [48].

According to Jackson [49], ten characteristics define an open system, *i.e.*, all open systems: 1) import energy from the external environment; 2) process and transform everything they receive from the environment; 3) export what they produce to the environment; 4) serve as new sources of energy; 5) have negative entropy, since they obtain more energy than they spend; 6) selectively collect in-

formation about their environment and their activities, and are corrected based on this information; 7) maintain their character due to the dynamic homeostasis; 8) are capable of differentiate and develop their structures; 9) have integrate functioning; 10) obtain the same effect from different events (equifinality).

Claude Bernard (1813-1878) was who proposed the concept of stability in biological systems, which was called *homeostasis* by Walter Cannon [50], in 1914. Canon's and Bernard's studies showed the role of adrenal *epinephrine* (or adrenaline) in the homeostatic process, while Hans Selye [45] demonstrated, in 1946, the adaptive importance of adrenal GC, analyzing the wide scope of action of these hormones in the body. Precisely, homeostasis is a property of all living systems, and several homeostatic mechanisms are active full-time to keep internal balance.

Selye [45] called the sum of all the systemic non-specific reactions of the body resulting from a long-continued exposure to stressor of *Syndrome of General Adaptation*. It is distinct from specific adaptive reactions, such as the development of the musculature following prolonged physical exercise and the immunologic and allergic phenomena. Syndrome of General Adaptation is divided in three different stages: 1) *stage of alarm reaction*, in which the subject experiences characteristic sensations from alterations in the internal equilibrium of the body; 2) *stage of resistance*, when the organism tries to adapt to the stressor, and 3) *stage of exhaustion*, which results from prolonged exposure to the stressor without occurrence of adaptation. Psychosomatic diseases are a result of the organic inability to compensate for stress. Selye emphasized the implication of the sustained high production of GC to the establishing of the exhaustion stage.

Thus, stressor stimulus initially provokes the *state of alarm*, due to the strong sympathetic discharge and consequent release of catecholamines, *norepinephrine* and *epinephrine*, from the adrenal medulla, which produce characteristic cardiovascular and metabolic effects. If the action of the stressor is of short duration or not intense, sympathetic and catecholaminergic effects can be able to maintain the internal equilibrium of the body. However, sustained exposure to the stressor action provokes the increased release of GC [45], establishing the *state of resistance or stress*. This prepares the organism to satisfy the energetic demand and to increase the general defense mechanism.

The state of stress is established when a wide, intense and prolonged reaction is necessary to maintain this internal balance. The stress hormone (cortisol, in human) is able to directly and indirectly initiate and control all stress mechanisms, seeking to maintain of internal equilibrium and adapt the animal to the action of the stressor or stressing situation. The stressor stimulates the state of stress and the forces generated by physiological responses (hormonal, neuromuscular, cardiovascular, inflammatory and immune) are resistance forces [39] [45] [48].

Almost every major life change can be considered as a stressors, *i.e.*, changes that require non-ordinary increase in metabolic dynamics to keep the organic balance and/or emotional. Thus, the stress state is characterized by energy ex-

penditure greater than that the body/mind is habituated in its daily life [51].

**Effects of the Stress Hormone.** GC have positive and negative effects in the dependence of their plasmatic level and time of exposure to stressor. In normal conditions, GC regulate with considerable degree of specificity the cellular differentiation in several tissues. GC can accelerate or delay the functional organic maturation. Normally, these hormones help in the general body growth and formation and maturation of organs, functioning together with GH (growth hormone), thyroid hormones, adrenal androgens and sexual hormones [52] [53]. However, GC excess can exert negative effects on body growth, inhibiting spontaneous secretion of the cited hormones and influencing negatively on cell proliferation [10] [54]-[59].

The most pronounced GC effect is its capacity to increase the blood glucose from hepatic gluconeogenesis, but it also plays a role in cardiovascular, nervous, endocrine, inflammatory and immunological responses [48] [60]. Very increased cortisolaemia causes: 1) the increase in plasmatic concentrations of glucose, amino acid and free fatty acid from cellular reserves; 2) decreased synthesis and increased catabolism of certain proteins; 3) alterations in hydroelectrolytic balance, circulatory hemodynamics and autonomic responses; and 4) decrease in inflammatory and immunological responses [61] [62] [63].

GC influence the phenotypical expression at synapses. It was observed that they increase the noradrenergic responses in cell populations predominantly cholinergic in its absence, evidencing its potential to change synaptic properties and to regulate neuronal plasticity [53] [64]. These observations are very important, considering that synapses are the base of neuronal processing.

On the inflammatory responses and immunological, GC play an important regulatory roles; They inhibit enzymes involved in the production of inflammatory substances, reduce the number of circulating lymphocyte (lymphopenia), eosinophil and neutrophil, and inhibit the antibody production [64] [65] [66] [67] [68]. High GC-exposure can produce significant atrophy on lymphoid tissues and contribute to the pathogeny of inflammatory diseases and to clinical progression in viral infections [67] [69] [70] [71] [72].

Indeed, mechanisms developed during the stress states may become pathogenic, depending on the following factors: 1) The stress intensity; 2) stress duration, since protein synthesis does not decrease during the first 24 hours after the increase of GC, and an immediate increase in DNA synthesis can be observed; 3) affective representation of the stressor; 4) nutritional status of the individual; 5) extension periods of rest and sleep [38] [55] [58].

Efforts have been made in the search for objective markers to assess the intensity of stress and its effects. In experiments with rats, stress has been measuring by blood levels of GC, especially corticosterone [54] [73] [74]. In humans, cortisol is a natural marker, which can be measured in the blood, saliva and hair [75] [76] [77].

In conjunction with cortisol levels, other biological measurements (such as salivary prolactin, vasopressin, blood pressure and heart rate variability) have been

considered useful to monitor the evolution of stress and validate stress reduction programs [78] [79] [80]. But it is important consider racial/ethnic and social class differences to study association between stress level and cortisol secretion. Physiological measurements may be convenient to indicate the stress in animals, however, the study of the state of stress in humans requires more detailed analysis [81] [82] [83].

### 3. Biological Systems and Internal Balance

Understanding the phenomenon of biological stress from the point of view of Physics requires analysis of the stress state in its specific aspects looking for conceptual convergences.

Based on the concept of stress and the physiological mechanisms involved and implications, we could say that a stressed organism is in “excited state”. This is a term commonly used in the context of atomic/molecular phenomenology [84]. In fact, during stress, the body is out of its “ground state”, and it is in a “higher energy level” or “excited state”. As expected for an excited molecule, the natural tendency of “excited organism” would be after some time go to back to its “lower energy state”. However, here are worth the following questions: *what would a biological ground state or lower energy state be? Does it make sense to talk about a ground state in Biology?*

#### 3.1. Ordinary and Stress Homeostatic State

In the search for answers to the questions above, we will start considering that each cell has its condition of maximum balance, that is, a condition in which its components work in their “ideal operating conditions”, thus spending the least amount of energy possible to maintain its functions. Undoubtedly, maintaining an “ideal” work rate in a cell requires certain conditions, such as the absence of morphological and metabolic errors. In addition, the environment must be able to meet all its chemical, physical and nutritional needs. That way, we could have a cell operating in “fundamental condition” ... Would that be possible?

But, these conditions are nearly impossible to meet. However, we can assume that each cell (or each part of the body) can have its own “lower energy state” in accordance with its morphofunctional conditions. This would be its state of higher internal possible balance, its “steady state” or homeostatic state. In this, the physiological parameters can vary within certain limits, being adjusted by immediate response mechanisms, which do not mobilize large energy resources. Variations out homeostatic limits call for intervention of more powerful and wide control mechanisms, which are not active in the ordinary steady state. Such mechanisms involve the mobilization of energetic reserves do not used in homeostatic conditions, such as gluconeogenesis and proteolysis to generate energy. At that moment, the state of stress or “excited” is established.

Despite the large increase in the energy consumption during the state of stress, such as occurs in the ordinary homeostatic state, *energy enters and leaves the system at the same speed, and physiological parameters remain within de-*

*fined limits, due to the continuous production of energy and matter* [49] [85]. However, it is important to consider that, extinguished the action of stressor, it is possible that living organism does not return to its homeostatic state before stress. In post-stress, depending on how long and/or severe the stress was, functional balance may be moved to another level, in which organic activity and energetic expenditure can be higher or smaller from the previous one.

So, we can say that the cell/organism is in an excited state during the stress and, and it may or may not return to the work regime prior to the stress period with the suspension or exhaustion of the resistance forces.

After prolonged stress, there is great chance of the organism starts operating in a regime of lower metabolic activity, with changes in the rate of transfer and transformation of energy/matter, and physiological deficits due to the depletion of mobilized resources [51]. Post-stress alterations can result in major imbalances and result in deep functional changes in tissues and organs [39] [54] [73] [74] [86], including endocrine, metabolic and immunological changes. There are studies shown that cytokines play an important role in these changes [87] [88] [89].

### 3.2. Internal Imbalance and Illness

The function of stress is to keep the biological system in balance, controlling the production and expenditure of energy and matter, conserving the catabolism-anabolism balance and taking into account energetic, structural and transport demands [90].

One of the important consequences of catabolism-anabolism disequilibrium is the cellular oxidative stress. This results from excessive formation of free radicals (substances with high oxidation capacity) due to an irregular balance between the formation rate of these radicals and the neutralizing capacity of arsenal of antioxidant enzymes. The mechanisms of oxidative stress interfere in cellular functions.

Much emphasis has been placed on nuclear and membrane changes produced by lipid peroxidation and cell protein degradation induced by oxidative stress. Due to their aggressive potential, free radicals have been identified as carcinogenic and atherogenic substances, and capable to induce neurodegenerative diseases (such as Alzheimer's and Parkinson's diseases) and aging [91]-[96].

In 2004, Epel *et al.* [96] studied the relationship between telomerase activity and telomere length in mononuclear blood cells from healthy women. Telomeres are repeated sequences of DNA that form the end (tip) of all linear chromosomes. Telomerase is a ribonucleoprotein enzyme (is a reverse transcriptase) that stabilizes the telomere length. This enzyme adds hexameric repeats to the ends of telomeres of the chromosomes, compensating the continued telomere erosion [97] [98]. Epel *et al.* [99], in 2006, observed lower telomerase activity and shorter telomeres in women with higher levels of perceived stress. The average telomere shortening was equivalent to at least a decade of additional aging compared with low stress women.

According Kiecolt-Glaser and Glaser [100], the studies of Epel and colleagues allowed to understand the link among chronic psychological stress, oxidative stress and telomere length since psychological stress can increase inflammation and oxidative stress [101]. It has been shown that the telomere attrition is accelerated by both inflammation and oxidative stress [102] [103]. There are several recent evidences indicating that telomeres and telomerase activity are particularly sensitive to oxidative damage and psychological stress [104] [105] [106].

More recently, other studies have discussed the impact of stress, especially psychological stress, on the aging process [107] [108] [109]. The important role that stress plays in senescence process has been demonstrated. In this process there is a gradual decrease in cellular functions and a consequent reduction in cell multiplication. It is a process linked to aging, in which the shortening of telomeres is a key mechanism [110] [111].

Increased rates of morbidity and mortality from chronic diseases of aging are found in individuals chronically exposed to psychological stressors early in life [112]. Some diseases related to aging have been linked to the action of stressors, and epigenetic alterations have been identified as an important mechanism that links stress to aging. In such alterations, environmental factors induce changes in gene expression, but the genetic sequence is preserved [107].

#### **4. Entropy and Biological Systems**

At steady state, the properties of any material body can be described by thermodynamics; and analysis of biological stress in this way can reveal other distinctive features of its nature.

The second law of thermodynamics is related directly to a concept widely discussed in Biology: entropy ( $S$ ) [113]. In 1865, Rudolf Julius Emanuel Clausius (1822-1888) introduced in Physics the concept of entropy, from the Greek *en-tropein*, which means “the transformative content” or “the content of transformation” [114].

Just like stress, entropy is a complex subject, and different ways have been used to understand its concept.

Entropy is an abstract dimension that represents the measure of disorder of particles in a physical system, as well as the measure of randomness and irreversible increase in energy in the universe. It is an entity involved in changes that occur in our universe constantly moving and transformation, being therefore difficult to represent it in a totally clear form [46] [115] [116].

According to the second law of thermodynamics, “the entropy of an isolated system not in thermodynamic equilibrium will tend to increase over time, approaching a maximum value at the equilibrium”, *i.e.*, the system reaches a state of maximum entropy.

As a function of the state, the change in the entropy of a system is determined by its initial and final states, being constant in reversible processes and, in irreversible processes, the total entropy continues to increase. That is, in a system in equilibrium entropy is high, and no spontaneous process can occur without in-

creasing the total entropy of the universe ( $S > 0$ , for spontaneous processes). In living systems, as all highly organized systems, entropy is very high. [115]

In *macroscopic thermodynamics*, the concept of entropy is related to the difference between the useful chemical energy and dissipated energy. Transferring an amount of heat to a system in equilibrium, the increase in entropy can be represented by  $\delta Q/T$ , where  $\delta Q$  is the energy flow into the system due to heating and  $T$  is the absolute temperature. The total entropy will be given by the integration:  $\Delta S = \int \delta Q/T$ , as defined by Rudolf Clausius [114]. The heating of system increases randomness of molecular motion and generating more micro-states possible.

In complex systems, entropy is determined by the number of random micro-states. The greater the number of possible microstates, the higher is the entropy [115] [117].

In *statistical thermodynamics*, the entropy is the measure of the degree of probability that a system will expand into different possible quantum states. In a system in equilibrium, entropy is maximized due to the loss of all information on the initial conditions, except for the stored variables. In view based on the probability Boltzmann (1872), the entropy of a macroscopic state is proportional to the logarithm of the number of microscopic states (states or density), is given by the equation

$$S = -k \sum_i p_i \ln(p_i) \quad (3)$$

where  $k$  is the universal constant of proportionality and  $p_i$  defines the individual probability for each microstate. Therefore, the statistical view shows entropy as the amount of uncertainty that remains in the system after considering its observable macroscopic properties. It leads to the idea that all dynamically ordered states are highly unlikely states, including life. Therefore, this view of the second law has been intensely debated [118].

The mathematical concept of thermodynamic entropy has been extended and interpreted in the light of Statistical Mechanics and Information Theory. These two entropy concepts present visible connections, and they play an important role in our discussion involving entropy and biological stress.

#### 4.1. Entropy in Statistical Mechanics and Living Systems

*Ludwig Eduard Boltzmann* (1844-1906) tried to explain the existence of a “high degree of organization” in the universe through an argument called the paradox of the brains of Boltzmann. According to this, the low entropy system is a random fluctuation in a higher entropy universe. Even in a quasi-equilibrium state, stochastic fluctuations are present in the degree of entropy. But there was much opposition to the arguments of Boltzmann [119] [120].

According to Erwin Schrödinger (1887-1961), there is no violation of the equilibrium equation of the second law, if we consider that living beings produce entropy at a rate sufficient to compensate for their own internal ordering, concentrating a stream of order on itself, because “*life feeds on negative entropy*”

[121] [122].

The problem of high improbability of spontaneous order started to be solved when *Karl Ludwig von Bertalanffy* (1952) showed that *that open systems can order itself by their ability to build their order by dissipating potentials in their environments* [123]. In 1977, *Ilya Prigogine* [124] called such systems “dissipative structures or self-organized” and contributed to the drafting of minimum production of the *Theorem of Entropy*, applicable to stationary states of non-equilibrium” [125]. This theorem gives a clear explanation of the analogy between the *stability of thermodynamic equilibrium and stability in biological systems, generated by dynamic equilibrium*, as expressed in the concept of homeostasis proposed by Claude Bernard. Thus, a living system self-organizes and continues self-organizing throughout its life, due to its metabolic dynamics [126] [127].

The concept of entropy was later extended by J.P. Lowe [127], based on the relevance of occupancy of energy levels, and H.S. Leff [128] provided a theoretical basis for interpreting the increase in entropy with the increase in energy dispersion due to rise of the number of microstates. In this case, entropy is associated with increased randomness due to interparticle spacing. For an ideal gas expansion in vacuum, for example, the molecules can take different forms (electronic, vibrational, rotational and translational) to distribute their energy, generating different entropies.

## 4.2. Information Entropy and Living Systems

In Shannon’s Information Theory (1948) the word entropy was included based in its concept in Statistical Thermodynamics, developing thus the information entropy. For Shannon, the number of distinguishable symbols in a communication channel is the number of distinguishable states in a system [129] [130].

The information entropy measures the uncertainty on the amount of information needed to represent a system. According Brillouin [131], acquiring information about the possible microstate (possible combinations of particles in possible energy states) of a system is associated with the decrease in entropy, since work is needed to extract information, and information removal leads to an increase in thermodynamic entropy. In that way, entropy is related to the amount of additional information needed to specify the exact physical state of a system, given its macroscopic specification. So, entropy can be also considered an expression of the lack of information about this state [132].

Information Entropy has also been used to display electronic properties as information functions for atoms and molecules. For Zhou *et al.* [133], Shannon entropy should contain all the information needed to adequately describe an electronic system.

The Functional Information Theory based on Shannon Theory has gained application in a wide range of studies in Biology and Medicine, including detection of gene-gene interactions, classification of biological compounds, and analysis of electrogram entropy maps in cardiology [134]-[143].

Using information theory, Ofria *et al.* [144] focuses on the selective pressures of molecular evolution and how they contribute to the development of robust and complex structures. Despite the information theory does not tell about information related to functions and mechanisms involved in cellular input-output, Lan and Tu [145] believe this theory provides a general tool able to analyze certain biological data.

In addition, this theory has suggested that genetic instability of repeated DNA sequences may be fundamentally related to the process of aging. According to Riggs [139], rather aging and mortality are the inevitable natural consequence of increasing informational entropy (decreasing redundancy) contained within the genome. Therefore, the information theory has progressing, and fundamental aspects of average entropy and mutual entropy mean in the open system dynamics has been presented [140] [141].

Thus, the view of informational entropy complements the thermodynamic view. In the first, entropy relates to the uncertainty of the information distribution and, the second refers about the loss of all information on the initial conditions in a system in equilibrium and entropy maximized.

## 5. Stress as a Principle of Nature

The present discussion aims to highlight the opposite roles of stress and entropy. While in the concept of entropy “*life as highly unlikely*”, corresponding to an amount of uncertainty on the existence or measure of the degree of probability of a system expands into possible different microstates, the stress becomes the *life highly probable*, opposing to the expansion of system and preserving the number of possible state and its existence.

We draw attention to the fact that, although manifesting in different forms, stress is always the same basic and intrinsic principle of living or not living systems. The preservation of life involves forces ranging from molecular to the mental level, which generate conservative/adaptive behaviors. Thus, we highlight a possible way to understand stress as a ***principle of nature***, considering the biological stress forces as a consequence of this principle wherein “*the order is produced in order to bring back to order in order to produce more order*”.

In humans, the corporal and mental stress is the macroscopic manifestation or the translation of cellular stress, which develops from stress at the molecular level [146]. Thus, the biological stress is the result of the combination of reactive forces developing on an increasing scale, from the microscopic to macroscopic scale, face to the possibility of internal balance disruption of the living system: tissues, cells, biomolecules. Stress forces trigger specific responses to sustain the dynamic homeostasis and preserve the order, which defines the “information contained in the life”.

From the thermodynamic point of view, the action of the stressor in a system tends to alter its entropy, since it changes its equilibrium and increases the randomness, due to the increased number of possible states. In that way, stress mechanisms try reduce the uncertainty about the initial state of the system, as well

as about the amount and distribution of information (genetic, and/or morpho-physiological information, in biological systems) needed to specify its exact physical state. Maximizing entropy leads to maximum condition of ignorance about this state. But the forces of stress, opposing the stressor, seek to balance the entropic forces and protect the information responsible to maintaining the ordered system.

Like entropy, stress is not uniformly distributed throughout the living body. Each cell or tissue exhibits a specific response to stressor [38], and the control of catabolism-anabolism balance seems to be a way of dissipating internal entropy [90] [126] [127].

In our dual universe, where randomness coexists with ordering, biological stress is opposed to randomness to keep the in dynamic equilibrium until adaptation is achieved. However, when stress exceeds adaptive limit, stressful or entropic forces overcome the forces of stress and the organic imbalance grows. Then, the exhaustion stage is installed [45], generating physiological disorder that can progress to disease.

As some works in the literature show, regardless of the stressor, biological stress can be studied in the light of Physics. Models of biological stress can be built based on internal changes (metabolic, ionic gradients, membrane repair, among others) generated by resistance forces and the amount of energy spent on these changes. Predictive models can be built, and computer simulations can provide information about the average responsiveness of the living system to a specific stressor [18] [19] [20] [21] [22] [30] [31] [32] [147] [148] [149] [150] [151].

Due immense diversity of living systems, the application of mathematical formalism to study stress in these systems seems impossible. But, the work of Epel *et al.* [96], cited above, showed that, like the non-living systems studied in Physics, intense and/or prolonged stress can “deform” structures in the biological system, as the shortening that they observed in telomeres.

Although it is a difficult task, the current knowledge on organic and cellular structures, interactions and mechanisms triggered by stress already allows drawing parallels aiming to model the biological stress based on Physics concepts.

## 6. Conclusions

By means of the review and comments above, we attempt to present an alternative view of the biological stress using concepts of Physics. In the state of stress, conservative forces are activated trying to preserve the order of systems, enabling their existence.

Considering the concepts of thermodynamic entropy and informational entropy, and comparing stress in living and non-living systems, we can see it as a *principle of nature* linked to the adaptability property of matter, as opposed to entropy. It is known that increasing the number of possible microstates in a complex system increases entropy, since it increases the uncertainty about the

additional information needed to specify the exact physical state of a system. By controlling metabolic processes (catabolism-anabolism) to decrease entropy, stress reduces the number of possible states into which the living system could evolve, preventing the loss of “life information”, preserving its characteristics and preventing its extinction.

The animal organism has several efficient mechanisms to maintain its general balance during stressful situations. This mechanism, however, can fail since the cellular responses depend on the type and intensity of stress.

The cell can cope with effects from the stressor, if it does not exceed its capacity to generate adequate protective responses to ensure its survival. Thus, as seen above, very prolonged stress has a destructive effect on tissues, because excess organic GC inhibits several activities, including hormone secretion, cell proliferation, immune responses and causes significant nervous changes.

It is important to remember that any “machine”, living or not, has its adaptation limit, outlined by its constitution and structure, and its mechanisms of interaction with the environment. The final changes, which result in an effective adaptation, must be processed within the speed limits compatible with the responsiveness of the “machine”. The compatibility of these speeds allows the relaxation of machine components, between one and another processing. Relaxation time is the period of time required for a system out of equilibrium condition to return to it. This time is essential for the equalization of intrinsic processes of the machine components, which defines a new ideal pace of work and the advent of adaptation.

Interestingly, within the known universe, natural eternity presents criteria that are impossible to achieve, even for a single simple cell, such as a protist cell, since all beings depend on the environment to live, but it remains constantly changing. This implies an almost continuous process searching of adaptation, which takes the organism away from its ordinary steady state.

It is a paradox that, in order to survive, animals reduce their life span by aging. When we say this, we are not forgetting to consider the genetic characteristics of each species, since the average life expectancy of an animal is intrinsic to its species. However, it is also important to remember that the characteristics of each species result from several mutations over time, which generates adaptive mechanisms that have increased their ability to deal with environmental stressors.

The loss of function of a species within its ecosystem or cells within an organ may be showing that the limits of the stress principle have been “transgressed”. That is, the intensity and/or the duration of the stress exceeded the capacity of the organism live to process information extracted from the stressor and reprogram its physiological mechanisms, activating its adaptability process, while its internal balance is preserved.

Understanding their origin, it may be easier to visualize the stress in its many forms and learn, in fact, to deal with it.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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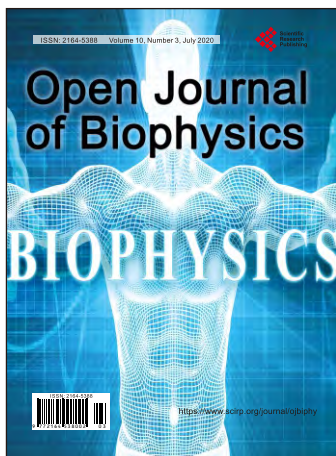
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