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The Second Law of Thermodynamics and Host-tumor Relationships: Concepts and Opportunities

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1. Introduction

The human organism continuously takes up nutrients to build up macromolecules and functionally active structures. On the basis of the first law of thermodynamics, the energy of nutrients is transformed, proceeding toward minimum entropy production and the release of heat and "waste products" in the open system. Part of the heat produced during exothermic processes supports the optimal efficiency of the endothermic biological reactions in the organism, and the rest is dissipated in the environment on the basis of the Second Law of Thermodynamics. In contrast with the living state, cancers live on the energy and mass of the organism as a parasite metabolizing and destroying the tissues of the organism according to the Second Law of Thermodynamics.

Schröedinger put the question of whether life is based on the laws of physics. He suggested that: chemical processes lead to entropy production, which is a direct measure of molecular disorder (1). At the end of his book, he summarized his view: "We must therefore not be discouraged by the difficulty in interpreting life by the ordinary laws of physics" (1). Where processes under conditions far from equilibrium correspond to an interplay between chance and necessity, between deterministic laws and fluctuations (2, 3).

During tumor growth, there are many differences between the healthy tissues and the growing tumor, including metabolic, structural and thermodynamic differences, for heat production. Both structural differences and heat formation can be used to follow the entropy differences between cancerous and nomal tissues. These entropy changes can be followed by various methods, e.g. histology and thermography. In general, the calculation of entropy production due to thermal fluxes based on temperature differences and, similarly, differences in other entropy-producing processes as driving forces are promising as potential targets for tumor demarcation (2-4).

Entropy production results from the transport of heat and matter between the two phases of the system and also from the chemical reactions taking place. Thus, the rate of increase of entropy production $\frac{dS}{dt}$ is a bilinear form of the rates of the irreversible processes and some functions of state, which may be called "affinities" or "generalised forces" as explained in Appendix A. S is entropy, T Temperature, V volume, Gibbs function, A affinity, n, number of species, I, II locations.

$$\frac{d_i S}{dt} = \left(\frac{1}{T^I} - \frac{1}{T^{II}}\right)\frac{d_i^I G}{dt} - \sum_\gamma \left(\frac{\mu_\gamma^I}{T^I} - \frac{\mu_\gamma^{II}}{T^{II}}\right)\frac{d_0 n_\gamma^I}{dt} + \frac{A^I \mathrm{v}^I}{T^I} + \frac{A^{II}\mathrm{v}^{II}}{T^{II}} \geq 0$$

The above can be replaced by Equation (3) from the Appendix and is as follows:

$$S d\mathrm{T} = -dG + Vdp + \sum_i \mu_i dn_i$$

A relatively simple form of the entropy production per unit time was expressed by Prigogine (3) below:

If the entropy changes in the two phases (at the border of the tumorous and the normal organ tissues) are compared as cancers' velocity, then the ratio between the two forms of tissue may be characteristic of the borderline, where an overlap in entropy production rate may be found between the normal tissues and the tumor. This can be considered a new target for demarcation (5).

Dissipative structures are useful models for *in vivo* experimental studies of the onset of tumors (3, 4), where individual tumour cell dynamics is seen as a fluctuation between molecular products smaller than a critical size and others larger than critical size, uncontrollably and permanently able to appear and develop through replication. The cell is then confronted with a population of cells that either succeed in destroying it or not. Cytotoxic cells can confuse dead tumour cells with living cells and as a result, the destruction of cancer cells becomes increasingly difficult. Here, the outcome of instability through fluctuation is growth occurring irreversibly in time, producing an evolution of a tumour whith the tumor developing a stealthy growth (6).

This simplest example of this kind of evolution is associated with the concept of structural stability: the competition determines the threshold of stability. The the new series of reactions then enter into competition with the previous mode of functioning of the system(7). However, chemical processes lead to entropy production, where processes under conditions far from equilibrium correspond to an interplay between chance and necessity, between deterministic laws and fluctuations (3).

If the structural fluctuation imposes itself, whereby the kinetics innovators is fast enough for the latter to invade the system instead of being destroyed, then whole system will adopt a new mode of functioning and its activity will be governed by a new syntax (4, 8).

Living organisms metabolize basic nutrients, converting their chemical energy to other forms of biomolecules and heat is produced as a by-product or waste energy that is dissipated to the environment. In the complex metabolic process maintained by the concentration gradients of the compounds, the transformed chemicals become incorporated into tissues of the organism. Leo Szilárd presumed, that an organism may behave differently from a mechanical system, causing a permanent decrease of entropy and thus violation of the Second Law (9). He then realised the possibility that the proposed arrangement

threatens the validity of the Second Law. It was thought that such a simple inanimate device could achieve the same result as that attained by the intervention of an intelligent being. The biological phenomenon of a non-living, theoretical device (Maxwell's "demon") that generates the same quantity of entropy as required by thermodynamics was examined along the same line of thought but the Second Law remains valid (9).

Thermodynamic properties such as entropy are of predictive value for further reactions and for the direction of the reactions. Organisms and their compartments are thermodynamically open systems; they have been analyzed by means of structural entropy. Such morphological studies give information about the entropy changes from a directed exchange with the environment, as considered by Kayser (10). When a solid tumor is embedded in healthy tissues, the entropy current is equivalent to the amount of entropy exported or imported through a boundary defined at a thermodynamic distance; this permits the introduction of the entropy concept to the processing of information (10).

Direction of Informational entropy

The Second Law of Thermodynamics does not allow the creation of entropy barriers, but it does not exclude changing the direction of some particular components of entropy flow from a tumor to the normal tissues in the close environment. The reversal of entropy flow in coexisting normal and tumor tissues may halt the tumor development due to reversal of the signal transmission as informational entropy in the tumor-host entity (11). The different entropy production rate between the normal and cancerous cells determines the direction of informational entropy current between normal and cancerous cells.

Energy requirements and time

The changes in the universe are continuous or permanent including the entropy increase content in the world, but "constant" things are transient in time. To preserve things in a given state, constant energy is required and the energy requirements for such preservation increase with time. One simple example is the system of melting ice (which can serve as an analog for very limited conditions for life). To preserve the transient state of coexisting ice cubes in water, we have to invest energy that will keep the temperature at around 4 °C, in order to avoid complete ice formation or complete melting of the ice cubes in the water. There is a permanent energy investment or requirement to maintain life, when the living object extracts energy from its environment. As in the case of melting ice cubes or completely frozen water, the system cannot be repeated or reinitiated. Similarly, the life processes cannot be reinitiated if the transient state is once interrupted by the cessation of energy expenditure. The instability of the melting ice system gives a good example of the opportunity for us to change the stability of the system by changing the direction of entropy flow by an increase of temperature. This opportunity does not mean that hyperthermia is applicable as a cancer cure: our previous calculations have demonstrated that the thermogenesis produced by cancerous tissue plays an insignificant role in the entropy production of cancer (12). However, the water–ice transition example shows that there are opportinities for modification of the direction of entropy flow in a thermodynamically open system.

There was a historical objection against the universal validity of the Second Law of Thermodynamics. This objection was embodied in the notion of Maxwell's demon, which appears again and again according to Szilárd. (The Maxwell demon catches the fast molecules and lets the slow ones pass, to gain energy at the expense of heat in a hypothetical engine with no mechanical structures that could lose energy in the form of heat). Thus it was

stated that, in a system left to itself, no perpetuum mobile of the second kind could operate, in spite of the fluctuation phenomena (9). No successful objection has ever been made so far. Thermodynamic differences between healthy and cancerous tissues suggest new strategies to contribute to improvement of the perspectives for the therapy of solid tumors and to reduce the development of their metastases (7).

The occasional question of what entropy actually implies has been answered given a very simple answer that entropy is the "shadow of energy" (13). The shadow of light is an illusion that can be conceived as a mirror-reflected picture of disordered material or chaos. The shadow of light is an illusion but the products of cancer in an organ can be considered functionally as inactive tissues that progressively reduce the specific physiological function of the organ and this process continuously develops, constantly gaining more space from the host and preventing the organ's function.

The development of the host-cancer relationship is a one-way road; it is an irreversible process in the coexisting cancer and host tissues once cancer begins. Cancer grows toward the maximum entropy according to the Second Law of Thermodynamics and lives on the negative entropy of the host in a superparasitic relationships if no external force field is applied (7). At the same time, the host develops toward the entropy minimum that is characteristic of the living state. At the border of the tumour and the normal tissues, the order-disorder transition area, the basic thermodynamic and biochemical changes occur. The developing tumor changes the minimum entropy production of the tissues toward maximum entropy production in this part of the organism functioning as a time delayed bomb. However, thermodynamic aspects of the composition and direction of entropy flow between cancerous and healthy tissues living in close proximity can be analyzed in reasonable detail. The questions arise as to what the known components of entropy production and what factors determine the direction of entropy flow from cancerous to normal tissues or *vice versa.* The main components are now listed below:

3. Components of the entropy program

1.	Cancer grows by invading into normal tissues but the opposite never occurs: normal tissues never invade cancer tissues.
2.	Tumors produce heat that is dissipated from the cancer to the normal tissues and can be regarded as a symptom.
3.	The low pH of cancer cells and the neutral pH of healthy cells produces a pH gradient between the two forms of tissues.
4.	At acidic pH, the ATP synthase activity of the tumor is further reduced in a vicious circle.
5.	The membrane potential differences between normal and cancer cells are responsible for maintaining some type of information flow.
6.	The electrogenesitic features of normal and cancerous tissues differ (cortical electrogenesis, muscle, retina, etc.).
7.	Enzymes and other biologically active compounds produced by the tumour cells which invade and survive carry information from cancerous to normal cells and mediate the nutrients and immunomodifiers.
8.	Dielectric structures are formed after transition from normal to tumorous cells (14, 15). In general, the direction of the entropy flow produced by the cancerous and healthy tissues is driven by concentration gradients, potential gradients, conduction, convection, diffusion, blood circulation, etc. (Table 1).

Thermodynamic forces drive fluxes:
1. temperature differences drive thermal fluxes. a. convection movement of biological tissues. b. conduction-related heat transfer. c. conduction-related matter transfer in the opposite direction (4. Glansdorff P. and Prigogine I. Thermodynamic Theory of Structure, Stability and Fluctuations, Wiley Interscience, New York, p.17, 1978,)
2. chemical potential differences drive diffusion currents: (disordered cytoskeleton, disordered mitochondria).
3. electric potential differences drive electric currents.
4. Gibbs energy differences drive chemical reactions, *e.g.* ATP can be synthesized from glucose depending upon the anaerobic glucose fermentation or on the respiration chain. Thus, the energy produced by one mole of glucose varies between 37 and 301 kcal/mol. At any rate, the high rate of glucose utilization of a tumor is greater than that of the normal tissues and this is exploited in tumor diagnosis by PET.
5. Viscosity differences make medium deformations.
6. Application of external forces can induce different entropy production in tumor and healthy tissue
7. Entropy differences drive entropy fluxes by determining the directions of processes. If different fluxes flow in the same direction, they result in flows or currents of information.
8. Chemotactic constraints in coexisting populations drive nutrient fluxes (Lotka Voltera type processes).

Table 1. Differences between cancerous tissues and normal tissues drive fluxes

The entropy flow carries information from cancerous tissues to the healthy tissues, which involves various fluxes carring information from the cancerous to the normal tissues, and also negative entropy from the healthy tissues toward the cancerous tissues. The entropy flow production and intensity are related to the accompanying convection to the biological tissues. The conduction relating to heat transport only can be neglected due to the homogeneity of temperature in the human organism. Conduction in the opposite direction to the transport of matter (cancer cells), may be called negative entropy. Since entropy flow is the flow of information from cancerous to normal tissues, only the contribution from items 1 and 3 listed above are now considered. The other items are considered later in this report.

Cancer can be considered as a type of energy parasitism where cancerous tissues divert or extract energy from the normal tissues (utilizing glucose, proteins and fats in various ways). In this way, the cancerous tissues transform the pathways of normal energy production and dissipate the excess energy as waste material. An aspect of practical importance in chemotherapy is the kinetic resistance: the chemotherapy acts mainly on proliferating cells whereas the resting cells survive. This reflects the intrinsic resistance of the DNA of the non-proliferating cells to drug-induced strand breaks. Pharmacokinetic resistance is manifested when drugs are administered at the "wrong time", when tumor cells are dormant, or are going through mitosis. The historically related criticism of ineffectiveness of cancer chemotherapy indicated the need to optimise treatment so as to avoid the continuous

administration of chemotherapy when tumor cells are in a resting or dormant state while the cells of the immune system will be eradicated as a consequence of the simultaneous adverse effects of tumor chemotherapy because these cells are renewing continuously.
A tumour comprises non-functional abnormal tissues, accepted by the immune system of the host as its own and not a foreign tissues but is a stealthy invader of the healthy tissues (15, 16). Tumour cells and tissues differ from normal cells in electric potential, electrogenesis, dielectric properties, electric conductivity, permittivity, impedance. For example disorder in the brain caused by a tumour means an entropy increase, and differences in entropy production rates between the two types of tissues determine the direction of entropy flow between the tumor and the healthy brain tissues around the tumor. The growing tumour competes for available energy sources. This may result in EEG changes in non-operated on individuals with a brain tumor. The focal slowing of the normal electrical rhythms close to the tumor are revealed as slow alpha and theta waves appearing in the projection area of the tumor. These changes are related to the high entropy production and the consequent import of negative entropy from the normal tissues. The growing tumor attenuates cortical electrogenesis and the electrical activity of the brain around the tumor tissues declines (17). Impaired electrogenesis means that a cancer has an electron deficiency which continuously reduces the electron pool of normal living tissues by oxidizing the living state, resulting in cancer. (In dielectric insulators or dielectric layers, the charges are fixed and are not free to move).
The extracellular matrix is less conductive than fibers or cytoskeleton components inside the cells. An applied electric field tends to restore the orientation of the dipoles and produces a field inside the dielectric which opposes the applied field. The conductivity describes the ability of the system to transport charge and the electric charge moves relatively freely. Permittivity characterises the ability of the material to trap or store charges. Factors tending toward the entropy maximum simultaneously result in a malignant state by invading host tissues, healthy tissues never invading cancerous ones.

4. What can be changed and how?

The key question is how the process of cancer development can be changed? One possibility is to overcome the kinetic resistance of a solid tumor or multiple tumors by consideration of the Gompertz growth model with chemotherapy included. The chemotherapy plus multi-drug resistance (MDR) -reversal compounds can halt the indefinite growth of cancer through the use of selective anticancer agents and selective inhibitors of ABC transporters (18). Since the Pgp17o glycoprotein responsible for the MDR of tumor cells also has physiological functions, it was reasonable to search for specific MDR-reversing compounds and highly selective antitumor drugs by using stereoisomers of certain active compounds. As a result of such experiments, tissue or organ-specific MDR inhibitors, combined with a tumor-specific anticancer drug result in strong synergy (18). The direction of entropy flow from tumorous to normal tissues in close proximity in the host was presumed to be reversed by such external forces based on the difference in entropy production of the two cell populations.
To maintain the normal signal transmission by particular protease inhibitors or by inhibitors of angiogenesis is another possibility. The blockade of various components of entropy production that mediate harmful by-products causing or inducing molecular or tissue disorders is a promising perspective. The other side of the coin is disruption of the quorum sensing mechanism (a population signal transmission) that triggers carcinogenesis (19). Nevertheless, we suppose that in the case of the host–tumor entity, the differences in

entropy production induced by various external interventions are able to change the directions of fluxes (Table2).

Effects of external force field on entropy dissipation
The rate of entropy production in tumor/normal cell is 1.1 without an external force field.
Application of a static electronic force field induces lower entropy production in thumor than in normal tissues.
A square wave electric potential increases the entropy differences by continuous switch on and off. The increase of frequency enhances entropy production. Applied square wave electric pulses produce more entropy in normal cells then in tumor cells. Tumor/normal ratio = 0.33
The effect has been exploited in the electrochemotherapy of skin cancer. (Rodriguez Cuevas Sergio et al. Archives Medical Res. 32,, 273, 2001Tisdale M J: J.Supportive Oncol 1, 159 (2003)
Delivery of electric pulses to solid tumors increases the susceptibility to anticancer agents due to transiently increased membrane permeability (Sersa M et al Cancer Res 55,3450, 1995. Belehradek M. et al Cancer 72, 3694, 1993).
Ultrasound-mediated chemotherapy with application of low output intensity 1 MHz, 2 W/ch2) increased the chemosensitivity of solid tumors to bleomycin (Tomizawa M et al Cancer Letters 173, 31, 2001).
The mechanism of action of cavitation, poration and re-sealing of cell membrans by acoustic pressure increases the intra-cytoplasmic concentrations (Luo L. et al . Diagnostic Pathology 2006, 1:43 doi:10.1186/1746-1596-1-43.)

Table 2. The possible effects of external forces on entropy dissipation from normal to tumorous tissues.

The entropy differences are maintained by different fluxes.

(I)	Temperature differences associated with thermogenesis and hyperthermia can produce an entropy maximum in tumours, but the normal tissues are more sensitive than tumour cells.
(II)	The diffusion current is driven by a chemical potential gradient, where a number of subcellular compartments are greatly reduced in cancer cells due to the dielectric layers formed.
(III)	Chemical reaction are driven by Gibbs energy, glycolysis being the main energy source[14] for cancer cells, which metabolise 10 times more glucose than normal cells. The roles of glucose metabolism and glycosylation are known. Anaerobic glycolyis provides the energy for cancer and the increased glucose catabolism is used as a basis of the identification of tumors by PET. The glucosylation of ABC transporters including MDR1, proceeds in cancer cells and in physiologically important transporters, such as the blood-brain barrier. The glucose-regulated proteins modify the drug resistance in cancer when upregulated (20). The organ-specific, *e.g.*, brain metastasis formation of breast cancer requires posttranslational glycosylation.
(IV)	The velocity gradient is driven by viscous stress. The change in electrochemical potential in cell membrane can change the dielectric structure and permittivity[14]

	beween the internal membrane surfaces. These structures are unable to provide free conduction electrons or can act as insulators.
(V)	The dissipation of entropy is due to the work performed by an external force field. An example is the exposiure of cancerous tissues to an electric field, which may increase the entropy production of the normal tissues above that of the tumorous tissues. This would mean that this intervention can reverse the direction of entropy current to enable its flow from normal tissues toward cancerous tissues. Another element of entropy production is the intensity of the individual fluxes and the sum of the "collected" entropy flows. Those effects determine the influence of the main pathway of interaction between the two co-existing entities. Heat dissipation from a tumor is mediated by the thermal flux driven by temperature differences. The heat production contains several parameters, one of which is diagnostic: it gives the metabolic rate of the lesion. Chemicals can diffuse in both directions, depending on their structures. The diffusion current between tumorous and normal tissues is driven by a chemical potential gradient. Chemical reaction rates are always driven by a Gibbs energy decrease: a velocity gradient coupled with viscous stress due to internal friction differences or dissipation due to work performed by external force fields.

5. The role of pH

With a pH gradient coupling with H potential differences, tumor cells preferentially convert glucose to lactic acid *in vitro*. Low intracellular pH values were demonstrated when pH electrodes were inserted into tumor tissues: the tumor was significantly more acidic than the normal tissues (8, 9, 21, 22). The membrane potential gradient is driven by potential differences between the cancerous and normal cell membranes. When tumour cells preferentially converts glucose and other compounds to organic acids, the intracellular pH increases. We can consider several examples of therapies:

a. Ultrasound

The pH differences between tumorous and normal tissues can be exploited in the reversal of the direction of entropy flow in the therapeutic application of the ultrasound irradiation of solid tumors when the entropy production of normal tissues may exceed that of tumorous tissues.

The aim of a good cancer outcome could be to change the direction of entropy flow based on pH, electric potential differences, *etc.*, where the most important contribution to the ultrasound absorption is related to the chemical relaxation and not shearing motions of medium molecules (10) and viscous stress or the heat loss due to conduction mechanisms because chemical relaxation (23) the basic contribution to the ultrasound absorption based on the pH differences (11, 12, 24).

In general, the pH measured in normal cells microelectronically is 7.2-7.6 while that in tumor cells is 5.6-7.2 which leads to healthy tissues displaying stronger ultrasound absorption than cancerous tissues. If we considered the relative difference between them to be 10%, then the difference in entropy production rate between tumorous and normal cells is 8×10^{-7} erg/degree/sec for an ultrasound power of 1 watt/cm on two types of cells, and lower for cancer at 2×10^{-7} erg/degree/sec (24). Naturally, decreasing the acidity in cancer tissue or increasing the acidity in normal cells would change the relative magnitudes of the entropy production rate of the two tissues and cause the reversal of entropy flow (24).

Acidic pH changes the conductance and dielectric properties of cancer cells, as discussed by Albert Szent-Györgyi (25).

In the host, the relationship, between healthy tissues and malignant tissues can be described by the Second Law of Thermodynamics. This defines the direction of physical and biological processes resulting in tumor growth. In the two living systems, the entropy dissipation is encoded in their genes; the exception is the response rate of dissipation to stress conditions affecting the organisms. As previously mentioned the negative entropy uptake compensating entropy production differs during life. Entropy production is a thermodynamic quantity for a living system. It depends on the quality of life conditions such as nutrition, physical exercise and the frequency of stress exposure. Entropy always increases for any non-equilibrium system due to the more disordered sub-cellular structures of the cancerous cells, with their different subcellular structures, following the Second Law of Thermodynamics (11, 12, 15). The information inherent in a cancerous cell is different from that in a normal cell. In living healthy cells, the free energy is high (increases) and their entropy is low (decreases) due to the altered metabolism at the expense of the environment (12, 16).

b. Electronic/Dielectric

Dielectric structures are formed in cells after malignant transformatiom, as shown by Thornton, who used inversion of Raman spectra to compare normal living cells and cancer cells[14]. With regard to induced dielectric structures, it was proved that chemical or other agents -which can change the electrochemical potential locally at the outer membrane- will produce internal dielectric zones. However, the transformation then subsequently requires that the polarisation P and membrane potential V change progressively to the Frölich metastable point in order for the transition to cancer occur. For example, a normal cell may not exhibit dielectric zones but P and V may never reach the metastable state and the cell will be benign. The progression to the metastable point involves successive mutations, (often quoted as about five) which could take a considerable time[14] . However, it does give time to set to act to avoid this progression.

The entropy production of healthy cells is lower than that of cancerous cells if no external energy input is applied to the tissues. However, when appropriate external energy is applied, the rate of entropy production of normal tissues may exceed that of cancerous tissues. Cancerous tissues develop toward the maximum entropy, but maximum entropy involves the total amount of energy not being available for work in the cells (11, 17).

As stated at the beginning of this report, we aim to review the essentials of the theoretical background of thermodynamics to introduce the reader to the application of the concept, with some examples of the combination of theory with multiple parameters of entropy production and the differences between healthy and cancerous tissues. Cancer and its surrounding normal tissues live together in a competition where the cancer cells are numerically inferior to the host cells. A small group of transformed malignant cells in a particular organ change the stability constraints of mass and energy flows in a thermodynamically non-equilibrium state. Conditions which favor the cancer cells or limit the growth or survival of their normal neighbors have therefore been studied.

In a breast cancer example, when normal human breast MCF10 cells or MRC5 fibroblasts were cultured *in vitro* in the presence of MCF7 human breast cancer cells in the absence of serum, the normal cells fed the cancer cells. In some experiments, serum as growth-promoting factor was replaced by the two sets normal cells. The results were defined by the competition factor F. The larger the competition factor, the stronger the exclusion effect

between the two types of cells. It was found that the competition exclusion between two kinds of normal cells is stronger than between normal and cancer cells *in vitro* in the presence of serum nutrients. That means that F is in the parasitism region and the cancer cells live in parasitic coexistence with normal cells. The case is different during starvation: in the absence of serum, F is lower than zero, *i.e.* this is a superparasitism region[7].

The competition between the two cell populations for nutrients may be dependent on activation energy, the intake of nutrients and the metabolism by cell populations. The differences in the network in signal transmission, the direction of conductance and subcellular compartmentisation may play a role in the coexistence of cancer, stromal and normal cells. In summary, there is some type of competition between the different cell populations. This can be explained partly by competition exclusion, if cancer cells have a smaller least resource requirement than normal cells[26, 27].

6. The role of nutrition

We presume that the entropy and energy contents of nutrients are also of importance in cancer development in open systems. The life processes need a continuous ingestion of low entropy and high energy-containing nutrients. The nutrients are converted to high entropy and low Gibbs energy-containing waste products that are excreted by the host. If the living state is maintained by the thermodynamically determined exothermic processes, and the non-equilibrium state by the continuous supply of the described nutrients, the question arises, whether the effects of highly processed food with a low free energy content and a high entropy state contribute to the increasing frequency of cancer, or whether the increasing incidence of cancer is a consequence solely of the increased and accumulating environmental pollution itself modifying the thermodynamic processes maintaining the normal living state of mankind.

We suppose that tumour cells are selected on the basis of their nutrient requirements. Cannibalism appears via autophagy which can occur for cancer cells to stay alive during dormancy. Cancer cells have different energy requirements than normal cells and finish or complete their development at an evolutionarily lower stage than complete differentiation. However, cell population systems operate at thermodynamic non-equilibrium, which continuously acquires free energy, heat and work from the surrounding. The life of cancer is ordered at the expense of disordering its surroundings, when cancer becomes a parasite of the living state. The mitochondrial activity decereases continuously in cancer. However, life is considered a physical phenomenon in which negative entropy is essential for maintaining the self-organization compensating the spontaneous entropy production according to the Second Law[15, 28].

This is an ideal parasitic relationship for cancer as a commensural type of co-existence whereby cancer and healthy cells can survive and grow. There is a tendency for the host to halt the parasite by the immune system from one side, and there is a tendency for the cancer to accommodate and to adapt the host and for example, avoid the immune system. Cancer colonises the host without provoking a response as functionally and immunologically inactive tissues propagate themselves and kill their host by increasing the ratio of functionally inactive tissues at the expense of the functionally intact tissues in the host. In the end stage the specific functions are reduced in the host as multi-organ system. The question is, what is the driving force of this process? Cancer cells can grow on a wide scale of nutrients from small molecules to dead cells or living cells, whereas healthy cells are able

to survive and grow only on a limited range of specific nutrients. The nutrient specificity of normal cells is limited to maintain the differentiated state, while cancer cells survive and grow under minimal nutrient conditions and in addition they are able to gain energy directly from the healthy cells and indirectly with the help of the stroma of the tumor. The simplest explanation is that the existing nutrient concentration differences and those of a large scale of substrates favor the slow overgrowth of cancer in the host when a transient immune deficiency can enhance the chance for tumor initiation and promotion. As a result, cancer has a selective advantage for growth due to the dissipation of the working structures and excess entropy. Another contributing factor can be the transforming growth factor produced by tumor cells inhibiting the growth of normal cells for their promotion. At a cellular level, after the initiation, deactivation of the immune system, the developing stroma and finally the metastatic invasion result in cancer. At the level of electrons, an electron acceptor blocks the electron donation from a purine or other molecules and the inhibited electron migration disturbs the conductance, resulting in restructuralization in the cells. Macrophage-like tumor cells are attracted, leading to repulsion in the absence of attractive forces.

There are changes in electromagnetic effects such as from the formation of dipole-dipole interactions and production of dielectric layers are produced and membrane and other oscillations are disturbed. The available energy does not satisfy the energy needs and the loosely bound cells continuously divide and subdivising can result because of the discrepancies between needs and availability. The high entropy production of tumor cells cannot be fully compensated by importing the negative entropy from the environment, and consequently the tumor growth is based upon the decomposition of normal cells and protein–lipid mobilisation by specific factors produced by the tumour[7].

7. Driving forces

The role of driving forces in cancer progression is unquestionable. The direction of entropy flow during parasitism is well defined. The irreversibility of the process can be explaind by competition for least resource requirements. This process consists of several components, such as accelerated glycolysis. Damage to the mitochondria, -or more exactly in the respiratory chain in tumor cells, - results in a compensatory increase in glycolytic ATP production in the malignant cells, together with a decreased level of oxidation of NADH-linked substrates. The mitochondrial defects contribute to tumor progression in several ways, such as by modified energy production, free radical generation and programmed cell death[28, 29, 30].

Proteolysis and lipid mobilization are energy sources in the host. The result is that the large majority of available energy sources in the host are governed and used by the tumor to support its survival and growth. As mentioned previously, this process can be considered as energy parasitism when the entropy production of cancer is compensated by energy withdrawal from the normal tissues in the form of negative entropy and high energy-containing macromolecules of the host. Consequently, the minimum entropy production of the living state becomes no longer sustainable. Enhanced glycolysis is the characteristic metabolism in the tumor[12].

The proteolysis-inducing factor produced by tumor cells appeared to fulfill the function of triggered muscle proteolysis, resulting in severe muscle protein degradatios[31]. Tumours also produce a lipid-mobilizing factor, which is associated with the progressive depletion of

adipose fat tissues and the depletion of skeletal muscle, and with changes in the body composition via induced hydrolysis of fats and triglycerides in adipocytes, protein degradation and protein degradation[32]. Also the tumor–produced lipid mobilizing factor causes stimulation of the protein synthesis. Different components of fluxes are essential in entropy production. The entropy flow from normal tissues to cancerous tissues carries information concerning the normal tissues, while entropy flow in the opposite direction carries information for the cancerous to the healthy tissues. As stated at the beginning of the report, the Second Law of Thermodynamics does not allow us to set up entropy barriers, but it does not exclude changing the direction of components of entropy flow from tumor to normal tissues. Entropy production in living cells contains more than 5 terms[12, 16].

In general, the relation between entropy and information quantity was defined by Schrödinger who revised the statistical meaning of entropy on the basis of the investigations of Boltzmann and Gibbs in statistical physics and expressed by entropy=k log D, where k is the Boltzmann constant and D is a quantitative measure of the atomistic disorder of the body in question. The differences in basic factors of entropy production between normal and cancerous cells determine the direction of fluxes, and those can therefore be regarded as targets of specific interventions in cancer therapy.

The rates of entropy production in healthy and cancer cells have been compared[12]. The differences were analysed via the comparison of selected factors, as follows:

1. The thermal flux driven by temperature differences, the production of energy and entropy loss due to heat dissipation.
2. The diffusion current driven by chemical potential gradients.
3. The chemical reaction rates driven mostly by decreasing Gibbs energy (affinity and glycolysis).
4. The velocity gradient coupled with viscous stress.
5. The dissipation of energy to the external field, resulting from the external work completed.

Many other factors contributing to entropy production were not included in those comparative studies, *e.g.* : the pH gradient associated with the higher acidity of cancer cells than of normal tissues due to the glucose metabolism, the membrane potential gradient driven by the different membrane potentials of normal and cancer cells, possible interactions between cells with different electric charges or resting membrane potentials; the information flux by conductance is driven by dielectric permittivity differences, where electronic energy bands are saturated, proteins are non-conductant; entropy currents driven by differences in entropy production by various processes.

The toxic effect of entropy flow plays a key role in the competition between tumour and host cells and determines the rate of tumor progression and the rate of cachexia. The cancer invasion has the first priority, while healthy tissues are not able to invade into cancerous tissues. Consequently reversal of the direction of entropy propagation can be a realistic goal as a therapeutic possibility. The intracellular pH of cancer cells is much lower than that of normal cells. The increased glycolysis resulting in metabolic acidosis was first described by Warburg 1956.

Dielectric layers have been demonstrated in proliferating cancer cells (14). The main point to be noted is that, the differences in the basic factors of entropy production between normal and cancer cells determine the direction of fluxes and consequently can be targets of specific interventions in cancer therapy.

8. Reversing the flow

What is the solution? How can we reverse the entropy flow? If we were able to increase the entropy flow from normal tissues, then the informational entropy of the normal tissues would counteract the informational entropy of the cancerous tissues.

1.	The extreme extent of glucose metabolization and heat production and the effects of an external force field on the studied 5 entropy production terms Appendix eq.3 have been discussed and evaluated from practical point of view in the case of external energy input, when the entropy production of normal cells can exceed that of cancer cells[10,11,12,15]. The direction of entropy flow would then be reversed and that leads to a blockade of the propagation of harmful information from the cancerous to the healthy tissues. Reversal of the directions of entropy flows by exposure to external forces appears to be possible.
2.	The artificial modification of acidity for cancerous cells can change the relative entropy production rates of the two kinds of cells and may lead to reversal of the direction of entropy flow. It can be supposed that modification of the basicity of a tumour leads to a standard free energy decrease and therefore entropy production would be lowered when the pH increases in a tumour. Modification of the glucose metabolism of tumors seems to be most difficult to achieve.
3.	Electronic energy bands are saturated and proteins are non-conductant in cancer. The conduction change due to the formation of dielectric layers in cancer cells is another possible factor for intervention[15]
4.	The conductivity differences between normal and cancerous tissues can be exploited as targets for intervention. The different sensitivities of cancer and normal cells to electric fields, *e.g.* square wave electric impulses, may result in changes in the polarisation of cancer cells, whereby they become more sensitive to external foces such as ultrasound or chemotherapy[11, 12].
5.	The application of low-frequency (1 MHz) and low-intensity (<1 W/cm^2) ultrasound can destabilize the connections of tumor tissues with their environment. Ultrasound absorption increases entropy production in normal tissues more efficiently than in tumorous tissues as a consequence of the more acidic nature of the tumour. Recent publications[23, 24] show that intervention is able to reduce the entropy flow from the cancer to the healthy tissues[23, 24].
6.	Alternating electromagnetic fields several volt/cm applied at low frequency appeared to have caused the reversal of entropy flow[24].
7.	An alternating magnetic field (10,000 Gs) induces additional entropy production in tumor cells by changing the entropy production threshold[15, 24]
8.	Modification of angiogenesis by an inhibitor reduces the nutrient support.
9.	Increasing temperature also appears to reverse the entropy flow direction somewhat and is thought to reduce the rate of entropy production from the heat flux, meaning some temporary benefit in therapy in some cases. However, mathematical and physics calculations have shown that entropy production due to heat is only a very small fraction of the total entropy production, and consequently the efficiency of hyperthermia as therapy is very low[12, 15]

Table 3. Some Possible Methods

9. Optimism and caution

The orderliness encountered in the unfolding of life springs from a different source. It appears that there are two different 'mechanisms' by which orderly events can be produced: the 'statistical mechanisms' which produce 'order from disorder', and a new one, producing 'order from order'. The Second Law appears to give a simple explanation. That is why physicists were so proud to have fallen in with the 'order-from-disorder' principle, which is actually followed in Nature and which alone conveys an understanding of the great line of natural events, and primarily of their irreversibility. We cannot expect that the 'laws of physics' derived from it automatically suffice to explain the behavior of living matter, whose most striking features are visibly based to a large extent on the 'order-from-order' principle. We would not expect two entirely different mechanisms to bring about the same type of law as -we would not expect a single solution of cancer treatments. We must therefore not be discouraged by the difficulty in interpreting life by the ordinary laws of physics. For that is just what is to be expected from the knowledge we have gained of the structure of living matter[2, 3, 13]**.** We must be prepared to find a new type of physical law. Or are we to term it a non-physical one, not to say a super-physical law, as the question was ironically put by Schrödinger[1]. This assertion, cannot fail to arouse contradiction. There are phenomena whose conspicuous features are visibly based directly on the 'order-from-order' principle and have nothing to do with statistics or molecular disorder. These calculations do not imply any statistics; they are based solely on Newton's law of universal attraction. The mechanical events seem to follow distinctly the 'order-from-order' principle, and if we say 'mechanical', the term must be taken in a wide sense[2, 13].

In a paper witten by Max Planck on the topic 'The Dynamic and the Statistical Type of Law' ('Dinamische und Statistische Gesetzmässingkeit'), the distinction is precisely labeled as 'order from order' and 'order from disorder'. The object of that paper was to show how the interesting statistical type of law is constituted from the 'dynamic' laws put forward to govern the interactions of single atoms and molecules[2, 7], where the understanding and the identification of the tumor escape mechanism are easier[16].

By combining morphology with kinetics of tumor development and textural, biological properties of tumor, the equations from thermodynamics can be used to illustrate the differences between healthy and cancer cells. The data allow appropriate calculations to be performed which induce the entropy concept to the processing of information collected by the analysis of various contributing factors. Healthy tissues display an efficient and stable way to perform the biological functions so as to maintain the lowest entropy level. Deviations from these values are reflected in differences in structures and functions between neighboring tissues in the thermodynamically open system of the host-tumor entity[12, 13, 16].

The entropy current is equivalent to the amount of entropy exported through the boundary between tumorous and healthy tissues. This is an appropriate measure of thermodynamic theorems[4, 26, 28] based on the evidence that the normal healthy state develops toward minimum entropy production, while a cancer moves towards the entropy maximum[1, 14, 15]. mc^2 is negative in nuclear fission, due to a decrease in mass, but positive for a growing mass of living organism[27, 28]. The difference between the two is the energy dissipation due to mass. The test of this came with the advent of nuclear fission, where energy appears to come from nowhere, but a term provided by Einstein readily maintains the validity of the conservation because the change in mass of the system, Δm is negative since the mass of the system decreases. While the First Law applies equally to living and to dead matter, the Second Law does not.

The First Law states that energy is conserved, while the Second Law states that, within the framework of conservation, one cannot have it any way one might like. It is a matter of everyday experience that certain processes do and certain processes do not occur in the world. Heat cannot be caused to flow from a cooler to hotter body without producing some other effect. Processes occur so as to progress from non-equilibrium toward equilibrium states; the direction of processes is therefore defined for a heat engine or a biological object operating irreversibly. For a heat pump or a heat engine or the diffusion of molecules through cell membranes, we may write irreversible when the total entropy changes are greater than zero. This means that the Secon Law is a sweeping generalization to the effect that, for any process, the sum of all the entropy changes occurring as a result of the process is greater than zero, and approaches zero in the limit as the process becomes reversible.

10. Mitochondria of cancer cells

One of the first attempts to destroy cancer was the idea of the selective effect of mitochondrial toxin for tumor cells. Papers have described mitochondrial toxins selective for tumor cells. The concept of a mitochondrial basis for killing tumor cells has existed since the early part of last century, based upon metabolic studies demonstrating general differences in metabolic control between cancer and normal cells[29, 30, 32]. Indeed, the metabolic disturbance in tumor cells is known. Metabolic disturbance due to abnormally high rates of glycolysis is demonstrated on a daily basis in the clinic through the fluoro-deoxyglucose PET scanning diagnosis of recurrent or residual malignant disease[33]. It was initially posited that mitochondrial oxidative phosphorylation was defective in tumor cells, and this initial insult led to gradual and compensatory increases in glycolytic ATP production as the central event of cell transformation. It was predicted that treatment producing a mitochondrial injury of a general nature would strike a greater blow against cancer cells, due to their already compromised respiratory state, than against normal cells. There is also the possibility that high rates of glycolysis may suppress respiration, known as the Crabtree effect, without implicating defective mitochondria[23, 24]. Interventions designed to attack metabolic susceptibilities of tumor cells have included glycolytic inhibitors (2-deoxyglucose), membrane pore activators (lonidamine), and thiol-active chemicals (arsenicals). More recently, screening of a combinatorial library of compounds based on natural benzopyran inhibitors of mitochondrial complex-I yielded several novel compounds with pronounced cytostatic effects against a cancer cell line panel[34]. It was calculated that cancer cells extract a much higher amount of glucose from the organisms than do healthy cells[12, 24]. In addition glucose-regulated proteins play an important role in the induction of MDR[20]. The mitochondrial susceptibility in cancer cells is interwoven with cellular metabolic control mechanisms. The mitochondrial uptake of particular toxins (F16 and other DLCs) also reflects the distribution across the plasma membrane, according to the plasma membrane potential, $\Delta\psi_P$, which may vary between cancer and normal cell populations[30,35,36].

New developments in chemotherapy are encouraging but the immunosuppression of chemotherapy is another important question considering the discontinuous tumour growth with reduced entropy production and the increasing import of negative entropy from healthy tissues. Attention to timing of therapies including chemotherapies is particularly important. In a dormant or resting phase of a tumor, the growth of the tumor cells is not really sensitive to the cytotoxic chemotherapy, but the toxicity toward bone marrow and other immune cells is continuous[15, 16, 33].

Living cells create an electric potential force between their various phases by three distinct mechanisms. Charge separation creates a potential of 120 to 145 mV between cytoplasmic and mitochondrial phases by unbalanced proton expulsion powered by the redox energy of the respiration chain. The resting potential of cells, which varies from -85 mV in the heart to -4.5 mV in red cells does not appear to result from an unbalanced flow of ions. Movement of an ion between phases entails three types of energy. The concentration work is that required to move an ion between phases containing different concentrations of ions. The electric work is that required to move an ion between phases with differing electric potentials. The osmotic work term is small and can generally be ignored. The measured resting potential between extra- and intracellular phases is approximately -85 mV, depending on the Na^+ or K^+ current flow. In the liver, the resting potential ranges from -28 mV to -40 mV, while in red cells the resting potential is about -4.5 mV. The resting potential between extra- and intracellular phases of cells should be thought of not as a diffusion potential, but rather as a measure of the electrical work. The use of intracellular KCl electrodes to measure resting electrical potential results from the existence of a mono-ionic Gibbs-Donnan near-equilibrium system between extra- and intracellular phases with the energy of ATP hydrolysis[34, 36]. In our experiments on resting cells in the presence of glucose concentrations increasing from 0.05 to 2.0% the fluorescence of R123 accumulation or uptake in MDR cells did not vary. MDR cells growing in the presence of various glucose concentrations displayed a somewhat elevated R123 uptake relative to the control. Acid diffuses from tumor to normal tissues as one of the component of entropy flow, making the normal tissues more sensitive to tumor progression and invasion.

10.1 Membranes and electrical potentials

The electric potentials of the membranes of resting (normal) and tumor cells are lower than those of normal cells. The membrane potential of proliferating tumour cells is somewhat lower than that of resting cells. The potential differences create a non-equilibrium state. These unique situations at the borderline of the two charged tissues and the resulting charge will be dissipated as bioelectric current, facilitating tumor invasion, or in other cases the ionized atmospheric electric weather fronts induce sensitivity to migraine in sensitive patients. If a larger area of the two cell populations with a larger difference in electric potentials is equalized in charges due to conductance, when the different charges are not isolated or the conductance is enhanced between them, this electric excitation may lead to epileptic seizures in a susceptible individual. The question arises of the consequences of entropy dissipation, the synchronisation of chaos, or the first step of the formation of a new highly ordered system. This is another example of entropy dissipation due to different extents of bioelectricity generation. In the case of brain tumors, the disorder in the brain caused by the growing tumour increases the entropy and reduces the nutritive proceses of the brain tissue. Differences in entropy production between the two kinds of tissues determine the direction of entropy flow from the tumor to the healthy brain tissues, with local slowing of the normal electrical rhythm in the neighborhood of the tumour, slow alpha and theta waves appearing in the projection area of the tumor. This finding should be related to the high rate of entropy production, and a negative entropy import from the normal healthy brain tissues can contribute to the attenuated cortical-electrogenesis around the tumorous tissues[21]. This *in vivo* observation can be supported by the superparasitic

nature of cancer cells in *in vitro* experiments[7]. Bioelectricity and conductance are well known and measurable in diagnosis via the heat function by ECG (in mV), in electromyography (EMG) (in mV), or in EEG (in μV) (36). At a cellular level, the differences in electric potential are much smaller and energy dissipation in the human central nervous system is 10^{-9} W per neuron. However, for comparison, the typical dissipation for a transistor has been estimated to be as small as 10^{-1} W [17, 37].

These differences can drive the bioelectric currents, and can contribute as a well-defined component of the entropy production, mediating information between healthy and tumorous tissues.

11. Combination treatments and need for maths and physics

Combination treatment of cancer may consist of electric treatment plus a chemotherapeutic agent, radiotherapy or surgery. The chemotherapy for recurrent or metastatic tumors results in poor response rates due to the MDR and/or the relative impermeability of cell membranes to chemotherapeutics. Combined treatment consisting of pulsed electric fields and chemotherapeutic agents has been used recently as electrochemotherapy[38, 39]. This treatment procedure relies on the physical effects of locally applied electric fields to destabilise cell membranes in the presence of chemotherapeutics. The electric pulses are used in attempts to deliver drugs locally to the cell interior and retain them there.

Topics in discontinuation can be demanding in mathematics and physics such as inverse problems for radiation treatment and in the dynamics of molecular motion in membrane penetration, Tumour growth is discontinuous and it is supposed that a discontinuity in entropy production takes place during tumor development. Discontinuity increases and decreases in the entropy indicate the stages where the tumor has to start importing negative entropy in order to survive and continue to grow. A sequence of progressive levels of density in tumors has been demonstrated by use of a new technique for the analysis of mammograms or computer tomography with graphic displays, reported together with new implications for therapy timing. The entropy production can be defined as heat dissipation, diffusion current glucose utilization, electric potential differences, membrane polarization differences and sensitivity to the application of external work, such as square wave electric potential exposure[40]. It is known that the thermodynamic entropy of a tumour is different from that of normal tissues due to a disordered structure of the cytoskeleton in the cancer cell the information contents of the two tissues must therefore be considered when the direction of entropy flows is planned to be changed, including mass transport or metastasis formation across the border between the normal and cancerous tissues[41, 42]. Informational entropy is a complex phenomenon in physics but can be defined logically with the aid of Information Theory. The large quantity of information includes some coincidences. Among the coincidences, there are some sequences. The sequences can transiently associated. Closely related associations can format premises. The overlap or condensation of related sequences can result in the formation of generalised analogies. The comparison of similarity analogies may lead to distinctions of differences. The disorder of tumors and the long-range correlations in ordered tissues are in competition with each other. Tumour cells break the ordering of processes in host and resulting propagation in existing structures. Their difference in entropy development increases with time. We presume that the entropy for the two different living systems increases monotoniously with time from zero to infinity, but

the differences are constant in time. The process of informational entropy flow thus introduces the arrow of time into cancer dynamics. There are opportunities to enhance the effectivity of chemotherapy, *e.g.* by using electrochemotherapy[38, 39], when a high intensity of electric pulses facilitates the uptake of chemotherapeutics into the cells[40, 43].
There is experience with the application of extracorporeal high-intensity focused ultrasound in producing the thermal ablation of solid carcinomas[43] and the microwave coagulation of solid tumours[44]. The electronic sensitisation of cancer cells to ultrasound, is an example of the combination of various physical effects for the treatment of solid tumours[45]. It has been shown that the exposure of tissue to high-intensity electrical pulses of short duration can induce reversible electropermeation and irreversible structural changes in the cancer cell membrane, in this way facilitating the uptake of normally impermeable substances into the cell [40, 43].

12. Conclusion

Under natural conditions, various entropy-producing processes exist in the four different types of cell populations coexisting in cancer cells, the stromal cells, immune cell and normal tissue constituents. Entropy proceeds from the cancerous toward the normal tissues. The large differences between the entropy of these four cell populations are the driving forces of the complex cancerous information flow from the tumor to the normal tissues. The numerous information fluxes coincide; among them, there are sequences based on the tendency of ordering toward energy utilization or mobilization from their environments. As the examples of external force fields suggest, there are opportunities to change the entropy production rates of coexisting cancer and normal cell populations (Fig. 1).
Alterating metabolic pathways of tumours shows promising approaches to achieve cancer therapies and publications have recently been reviewed[46]one new opportunity is being developed in Australia[47], particularly relevant to melanomas. It involves changing membrane potentials of tumour cells before reaching the metastic state so as to enter a new metabolic pathway, which, under pH control, can enter a further pathway chosen to either avoid a metastatic state or delay it to allow other therapies to gain advantage. Another opportunity is to induce cellular immunity, or an antipromotion-like mechanism to demarcate the cancerous tissue or stroma formation, resulting in the inhibition of negative entropy inflow as nutrient import from the healthy tissues.
In a reverse mode what are the prospects for the reversal of the entropy flow from tumorous to normal cells? Could we enhance the entropy production of the normal tissues around the tumour, to provide entropy flow from the normal tissues to the cancerous tissues while carrying the information from the healthy tissue toward the tumour. If, for example, the ultrasound absorption and entropy dissipation were made greater in normal than in cancerous tissues, the direction entropy might be reversed. Application of external forces may therefore give us hope that we can halt the progression of cancer or at least halt progression to metastasis for new therapies to be effective.

13. Perspectives to reverse the direction of entropy flow

As mentioned above, let us consider an entropy flow from normal tissues to tumorous tissues carries the information on the healthy tissues toward the tumor.

The first tems of entropy production contribute to a higher rate of entropy production for cancerous cells than for healthy cells; however, the situation is different for the chemical effects term, on application of an external force field.

Ultrasound absorption and dissipation in normal tissues is greater than in cancerous tissues, and consequently the direction of entropy flow can be reversed by exposure to an external force field such as an electric field or ultrasound. Low-frequency and low-intensity ultrasound is weakly absorbed in biological tissues (when the induced temperature increase can be neglected): consequently the effect of entropy production on non-damaged cells can be followed independently from temperature effects.

Entropy production due to exposure to a square wave electric potential is higher for normal tissues than for cancerous tissues (pulse frequency and field strength). Square wave electric potential-induced entropy production is comparable to chemical reaction-induced entropy production.

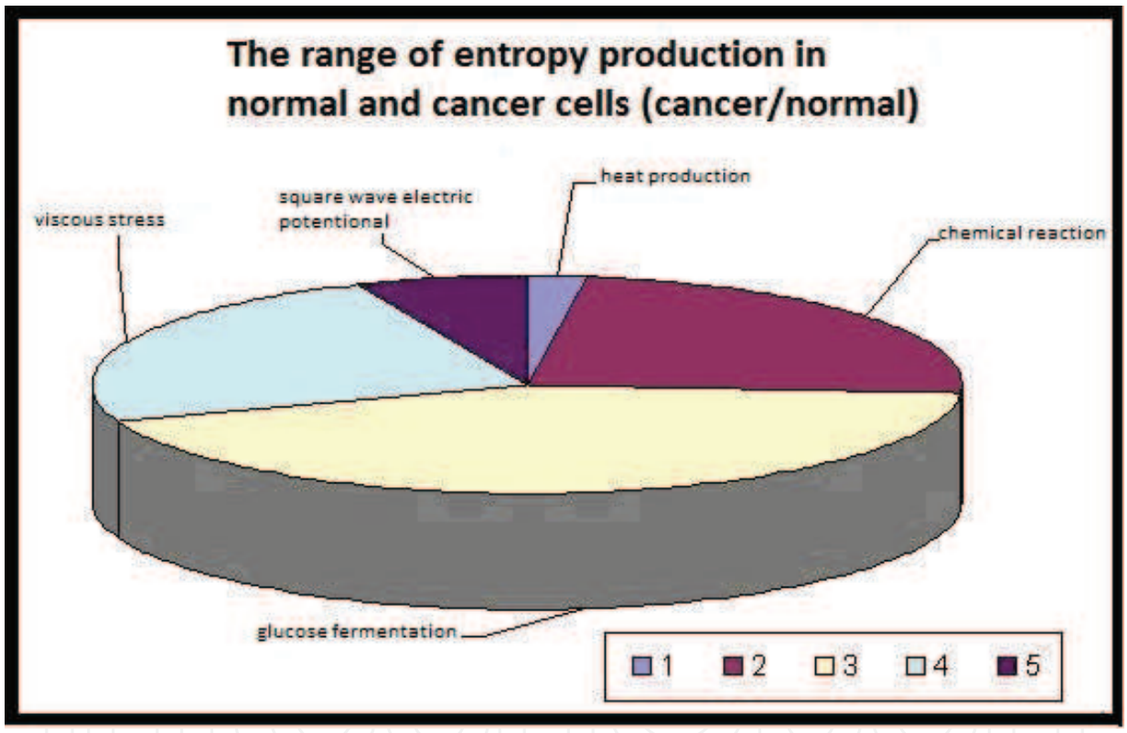

Figure 1. The ratio of entropy production between normal and cancer cells

Entropy production results from the transport of heat and matter between the two phases of the system and also from the chemical reactions taking place. Thus entropy production is a bilinear form of the rates of the irreversible processes and some functions of state, which may be called "affinities" or "generalised forces".

A relatively simple form of the entropy production per unit time was expressed by Prigogine (Prigogine I: Introduction to Thermodynamics of Irreversible Processes, Interscience Publishers, Division of John Wiley and Sons, New York, London).

If the entropy changes in the two phases (at the border of the tumorous and the normal organ tissues) are compared regarding the difference in velocity of change, the ratio between the two forms of tissue may be characteristic of the borderline, where an overlap in

entropy production rate may be found between the normal tissues and the tumor. If so, this can be considered a new target for demarcation.

14. Appendix

14.1 The second law and biochemistry

Gibbs "free energy" (thermodynamic potential) G is the function of most use in biochemistry and is the part of the energy which can be used for performance of work.

$$G = \mathrm{H} - \mathrm{T}S \tag{1}$$

The "total" energy H (heat content or "enthalpy") is the sum of the "free" energy, G and a function $\mathrm{T}S$ of the entropy S (ie the bound or unavailable energy which is present because of the chaotic motion of atoms and molecules.

The Second Law of Thermodynamics states the universal tendency of energy to become unavailable. Equation (1) defines G for an isothermal system at constant pressure which may gain or lose heat energy. The Second Law requires a net increase in entropy for any process in such a system together with its evniromnent. Because entropy can be transferred from the system to the environment the actual system can then have a decrease in entropy. However, an isothermal system at constant pressure must suffer a decrease in free energy. In an equilibrium state free energy has a minimum value and the difference ΔG in free energy between the system's actual state and its equilibrium state is, in effect, a measure of the system's tendency to change. At any given temperature T the difference in entropy ΔS and, the change in ΔG and $\Delta\mathrm{H}$ are related from equation (1) as $\Delta H/\mathrm{T} = \Delta G/\mathrm{T} + \Delta S$.

The Second Law requires an overall production of entropy from the environment and system, ie

$$\Delta S(e) + \Delta S > 0 \tag{2}$$

Where $\Delta S(e)$ is the increase in entropy of the environment.

It is a straightforward matter to define E, volume V and chemical potential $\partial G/n_i$ in terms of G, T and pressure p together with the number of chemical species n_i as

$$Sd\mathrm{T} - dG + Vdp \sum_i \mu_i \, dn_i \tag{3}$$

Reference: Bray H.G. and White K., Kinetics and Thermodynamics in Biochemistry, p77 (J2A Churchill) London, 1966.

14.2 Dissipative structures and the second law

With regard to the basic equation (3) it is of importance to note that any state of non-equilibrium associated with the system can be described by the same variables as used in an equilibrium state and they are governed by the same equation of state ie local equilibrium hypothesis simply means the validity of the Gibbs Law for irreversible processes. The summation term $\sum \mu_i dn_i$ where μ_i is the chemical potential of the component i . For each chemical reaction the affinity $\mathrm{A}j = -\sum \frac{v}{ij} \mu_i$ where the v_{ij} are stoechiometric coeffecients

[see Glansdoff P., Energy evolution of complex networks of reactions, p41-54 in Living Systems as Energy Converters, (Eds R. Buvet, M.J. Allen and J-P Massue), North Holland Publn, Amsterdam, 1977].

Auto-catalytic or feedback effects in a sequence of coupled chemical reactions may generate chemical instability. Catalytic effects in the kinetic equations can lead to a critical state beyond which a completely new behaviour may actually appear. The system still evolves in accordance with the Second Law of Thermodynamics but may not, in general, still comply with the minimum entropy production theorem. A new internal organisation in the system can become more orderly than those of the thermodynamic branch and are then called dissipative structures including spatio – temporal "chemical clocks".

15. Acknowledgement

The authors thank to Prof. Shlomo Ben Effraim and Prof. Liaofu Luo for discussions on questions the differences in entropy production of normal and cancerous tissues, and discussions on relationships concerning modification of the direction of entropy flow from aspects of electrobiochemistry. This work was supported by the Szeged Foundation of Cancer Research.

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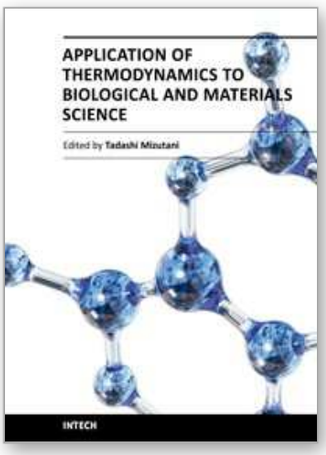

Application of Thermodynamics to Biological and Materials Science

Edited by Prof. Mizutani Tadashi

ISBN 978-953-307-980-6
Hard cover, 628 pages
Publisher InTech
Published online 14, January, 2011
Published in print edition January, 2011

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How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Joseph Molnar, Zoltan G. Varga, Elysia Thornton-Benko and Barry S. Thornton (2011). The Second Law of Thermodynamics and Host-Tumor Relationships: Concepts and Opportunities, Application of Thermodynamics to Biological and Materials Science, Prof. Mizutani Tadashi (Ed.), ISBN: 978-953-307-980-6, InTech, Available from: http://www.intechopen.com/books/application-of-thermodynamics-to-biological-and-materials-science/the-second-law-of-thermodynamics-and-host-tumor-relationships-concepts-and-opportunities

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