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# Cancer self-remission and tumour instability – a cybernetic analysis

# Towards a fresh paradigm for cancer treatment

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***Abstract*** *Aims to investigate the causative factors and clinical applicability of spontaneous regression of malignant tumours without treatment, a really paradoxical phenomenon with many therapeutic potentialities. Analyses past cases to find that the commonest cause is a preceding episode of high fever-induced thermal fluctuation which produces fluctuation of biochemical/immunological parameters. Using Prigogine-Glansdorff-Langevin stability theory and biocybernetic principles, develops the theoretical foundation of a tumour's self-control, homeostasis and regression induced by thermal, radiation or oxygenation fluctuations. Derives a threshold condition of perturbations for producing regression. Presents some striking confirmation of such fluctuation-induced regression in Ewing tumour, Clear cell cancer and Lewis lung carcinoma. Using experimental data on patients, elucidates a novel therapeutic approach of multi-modal hyper-fluctuation utilizing radiotherapeutic hyper-fractionation, temperature and immune-status.*

The spectacular phenomenon of Spontaneous Cancer Remission persists in the medical annals, totally inexplicable but real. From time to time patients turn up with advanced cancer beyond the possibility of cure. The patient is sent home to die, only to turn up again ten years later free of disease. But no one has any idea of how it happens. If thousands of patients have succeeded, medicine can learn to accomplish the same ... surely ...? (Lewis Thomas, MD, Sloan Kettering Cancer Centre 1983).

## Introduction

The unexplained paradoxical phenomenon of Spontaneous Cancer Remission, Prolonged Arrest and Tumour Dormancy, appears to be a perplexing case in the tumour stability-instability behaviour. A MEDLINE search (1966-92) yields 11,231 references to the terms "Spontaneous Regression" or "Spontaneous

Remission". *This anomalous behaviour requires a revision of our understanding of cancer: cancer is not invariably a progressive or fatal disease.* There are cases in which the tumour is in a meta-stable state of prolonged arrest for ten to 15 years (Everson and Cole, 1966; O'Regan and Hirschberg, 1992). Rohdenburg (1918) has hinted at the probable factors behind spontaneous regression and concluded that the most likely cause was high prolonged temperature or hyperthermic condition, e.g. 104°F fever for over a week. It is thermodynamically known that the higher the temperature, the greater the statistical fluctuation in a system. Cybernetics and synergetics emphasize the importance of small fluctuations which can drastically alter the behaviour of systems, whether physical, chemical or biological (Nicolis and Prigogine, 1977; Horsthemke and Lefever, 1984).

Majumder (1979), in the first Norbert Wiener Award paper, developed a unitary cybernetic approach of action and self-organization in biological and physical systems. On the other hand, in the recent Wiener Award, Prigogine (1999) has underscored the new nonlinear paradigm of instability and change. The well-known *Glansdorff-Prigogine Stability Principle* indicates that an open nonlinear system may become unstable at an appreciable distance away from stationary state, by means of sufficient non-equilibrium fluctuations. The formalism of bio-cybernetics of immuno-modulation and non-equilibrium bio-thermodynamics has become an important aspect of a systematic and integrated perspective on the problem of cancer and tumour biology. Present day clinical medicine and oncology has been almost exclusively concerned with the tumour and with the consequent aggressive ways to "attack" the tumour. Not much attention has been paid to a proper systems perspective and cancer researchers have generally neglected (what should be) the main point of concern, namely the organism, i.e. the host or the patient. The great advantage of the cybernetic and systems approach is that it approaches the problem of malignancy from the orchestrative interplay of the dual systems:

Tumour (the malignant subsystem) ↔ Host (the organism).

## Systems theory and cybernetics in cancer biology

### *Systems theory*

The approach of systems theory envisages that the problem between the interaction of the microsystem (the tumour) and the macrosystem (the organism) should be given critical attention, including the examination of the interaction shown by the symbol "↔" in the scheme presented just above. Indeed the systems theoretic perspective to immunolgy, oncology and cancer biology has been pursued by a number of investigators (Belair *et al.*, 1995; Mohler *et al.*, 1980). We may mention that the systems pioneer Bertalanffy (1970) himself initiated this approach as a mathematical biologist; the Bertalanffy equation is used for the study of growth in animals and tumours.

### *Cybernetics*

In parallel with the application of systems theory to oncological disciplines, cybernetics have also contributed to the analysis of the problem of progression,

regression and immunological regulation and control of tumour (Murray, circa 1995; Perelson, 1988). In fact we have investigated this research problem and the therapeutic approach being developed here is adapted from our earlier works (Roy and Sen, 1994; Roy *et al.*, 1995, 1996, 1999, 2000). We have explored the application of (a) the $C^3$ approach of cybernetics, viz. control, communication and computation to the problem of tumour growth and recurrence; (b) immuno-modulation for tumour regression (Roy and Das, 1995). We have also applied the systems approach of graph theory to determine anti-cancer activity in drug design (Chaudhury *et al.*, 1993).

## Energy metabolism and thermodynamics of malignant tissue

As the study of living processes was a main inspiration for the development of irreversible thermodynamics, the investigators of the subject also focused their attention on the study of irreversible growth in animals, such as tumours, hormonal disorders etc. Actually Prigogine way back in 1945 explored the possibility of applying irreversible thermodynamics to tissue growth. Subsequently Prigogine's groups in Brussels and Austin have developed the major area on non-equilibrium thermodynamic basis carcinogenesis and tumour growth, one of the major efforts at the Brussels centre coming under the purview of the National Foundation of Cancer Research. On the other hand, the German Nobel Laureate physician and biothermodynamist Otto Warburg developed the basic foundation of energic consumption and metabolism of tumour cells in the 1930s-1950s (Warburg, 1960). It may be noted that earlier biochemists like Crabtree and Pasteur had developed the concept of reciprocal bio-energetic effects which have a relation to cancer metabolism and energetics (Pasteur Effect and Crabtree Effects):

*Pasteur effect (-ve)* →

Oxidative Phosphorylation ←——————→ Reductive glycolysis.

← *Crabtree effect (-ve)*

## The bio-cybernetic aspect of evolutionary history of cancer

The evolutionary origin of cancer, as an irreversible proliferative activity of a cell, is a really fascinating problem for evolutionary oncologists as well as biocyberneticians. At what point in evolutionary time did cancer become the aggressive remorseless progression towards fatality, as seen in higher animals, losing the tendency of remission and self-control that we often see in tumours of lower animals? From the study of veterinarians it is apparent that cancer has a long evolutionary history. Some lower invertebrates such as Annelids which evolved 550 to 650 million years ago show evidence of neoplastic growth. We have analysed the percentage of fatalities occurring due to cancerous growth in various species of animals after the tumour has been detected. One thing has become clear to us, which is that, as animals evolved progressively, the aggressiveness and irreversibility of tumours increased. The more life advanced upwards, the more it lost the power of regeneration, regulation, and

repair whether of wounds or tumour. Earthworms can be bled 50 percent of their fluids and they survive, whilst man cannot tolerate bleeding above 15 percent.

Conversely, as we descend down the evolutionary ladder, the more the ability for regeneration and repair or regression of tumour increases. For instance, leukaemia/malignant neoplastic proliferation of leukocytes/haematocytes occuring in cold-blooded invertebrates like molluscs, as snails, which appeared about 500 million years ago. However, 74 percent of such molluscan cancers spontaneously regressing, only 26 percent becoming fatal (Kaiser, 1994). In other words, as organisms evolved, cancer became more irreversible and obstinate and less remissible. We also observe that tumour progression and aggressiveness increased much more from warm-blooded vertebrates, e.g. dinosaurs and pre-mammals which appeared around 230-250 million years ago, in the Permian age of the Palaeozoic era. This is evidenced by observation of aggressive malignant involvement of their fossil bones, e.g. tumours as osteoma/chondroma/osteoclastoma and osteosarcoma. Correspondingly, cold-blooded animals, like reptiles and snakes, show considerable propensity to reduce the rate of tumour progression after tumorogenesis has started, even for serious tumours such as melanoma, which is fatal to warm-blooded mammals (Frye, 1995). Two questions naturally crop up:

(1) Are aggressiveness and irreversibility of cancer a similar price that higher vertebrates have to pay for their thermal stability or cybernetic thermoregulation and increased energy metabolism?

(2) And, if so, can artificially-induced thermal de-stabilization, or temperature oscillation or fluctuation and system perturbation, have any therapeutic part to play in the reduction of aggressiveness of cancer?

## The methodology: systems approach of stability theory and tumour de-stabilization

During recent decades, the disciplines of cybernetics, nonlinear dynamics, stability theory and synergetics, have emphasized the importance of small fluctuations which can drastically alter the behaviour of systems, whether physical, chemical or biological (Prigogine, 1977, 1999; Belair *et al.*, 1995). The study of such transitions is one of the most fascinating fields of cybernetics and biophysics, especially neurocybernetics and immunodynamics. They have enabled a unified vision of the laws which govern the dynamics, control and instability in biological systems (Abraham, 1994). A major achievement has been the notion of phase transition towards instabilities which occur in nonlinear systems such as biological or biochemical ones. Such instabilities have been known from the turn of the century. Classical examples are Belusov-Zhabotinski reaction in self-oscillations and Lotka-Volterra interaction in ecosystems. Stability of biosystems is subsumed under the mathematical theory of stability in cybernetics.

In the Wiener lecture in *Kybernetes*, Majumder (1979) has shown that there exist various approaches to biocybernetic systems, all having historical roots in analytical mathematics, e.g. Lyapunov - Poincaré theory of differential equations, Nyquist control analysis and systems engineering. Using a Systems Theory approach, Roy (1980) has attempted an analysis of tumour de-stabilization. The Brussels school has pursued the stability problem elaborately, enunciating a new theorem of thermodynamics (Glansdorff and Prigogine, 1971):

> *Glansdorff-Prigogine Stability Principle.* This indicates that open nonlinear system may become unstable at an appreciable distance away from stationary state, by means of sufficient non-equilibrium fluctuations.

This theorem is the basis of our approach. We have explored the principle's applicability in several other biological problems (Roy *et al.*, 1993, 1995) including the problem of spontaneous regression and its therapeutic applicability, as cited earlier. These investigators, comprising physicians, biologists, engineers and mathematicians, have developed a rigorous focus on medical cybernetics and biosystems at the Institute of Cybernetic Systems and Indian Statistical Institute, Calcutta. Apropos these authors (Roy, 1980; Majumder, 1975, 1979), Cybernetics, along with Systems Theory, forms a universal theory of action, and is applicable to the full range of the life sciences, e.g. neurology, immunology, ecology etc. Observe that extrinsic and intrinsic environmental fluctuations of different modalities – such as temperature, pH, oxygenation ($pO_2$) and radiation inputs – seem to have a considerable effect on:

(1) Macroscopic properties of nonlinear bio-systems, e.g. elimination of predator-prey systems;

(2) Microscopic properties of the organism, such as extinction of cancer population and tumour instability.

Substantial work occurred in recent decades regarding the importance of explicit and implicit fluctuations of environmental or tissual parameters (Horsthemke and Lefever, 1984; Belair *et al.*, 1995).

## From neuro-computation to immuno-computation: a $C^3$ component of immunocybernetics

Recollect that computation or information processing is one of the main focuses of the $C^3$ formalism of cybernetics: control, communication and computation. Through such a cybernetic perspective, we propose to explore the stability of immunodynamic systems such as a tumour. Even though they are vastly different structurally, both the nervous and the immune systems are comparable functionally, as they deal with the same currency, namely information. Hence, a better insight into cancer immunology and tumour regression may be obtained by applying the formalism of information theories developed elsewhere, as in computer networks. The great potentiality of application of network analysis to immunology has been recognized by Jerne's

1984 Nobel Lecture. Jerne's (1974, 1984) investigations have initiated the subject of non-linear immunocybernetics, viz. the collective synergetic emergent behaviour and regulation in the immune system network as generated from the component cellular elements, which display adaptive self-organization and characteristics of a typical complex system.

Like the neuronal system, the immune system learns new information, perceives the environment (antigenicity), recalls previously learned information and then makes decisions on action, that is, displays the operations of cognition, intelligence and the "perception-action cycle" so familiar to neuropsychologists (Figure 1). The immune system (B-cell lymphocytes or white blood cells) can behave as an alternative biological model of an intelligent machine, in contrast to the conventional model of neural system (neurones); i.e. lymphocytes can substitute neurones for modelling intelligence. Parallel Distributed Processing (PDP) can furnish a basis of such intelligent networks,

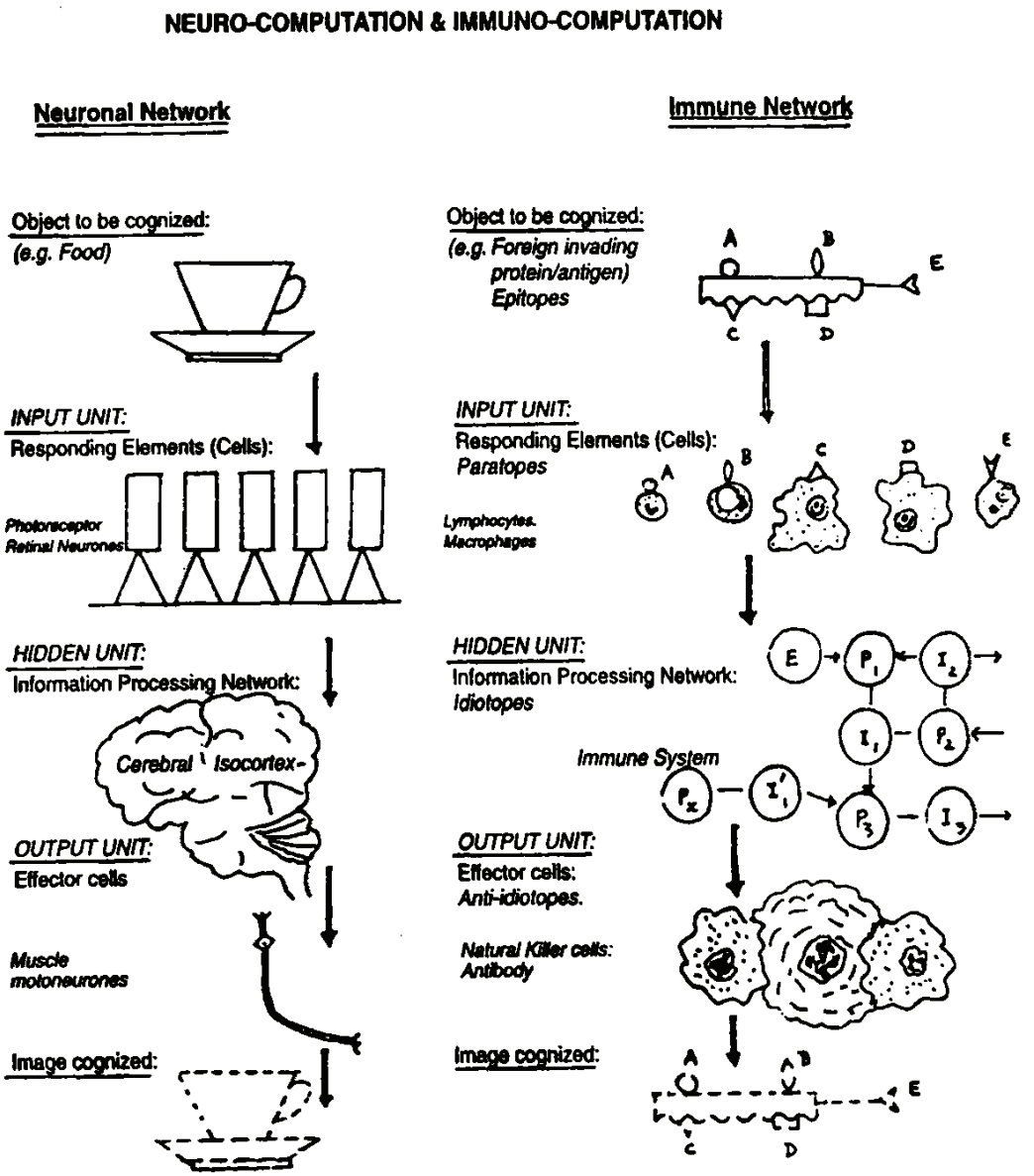



Figure 1. Neuro-computation and immuno-computation: a comparison – the immune network as an alternative prototype of an intelligent machine, in contrast to the conventional neural network model. The input, hidden and output units of the Parallel Distributed Processing (PDP) template are shown for Neuro-cognition and Immuno-cognition which generate the corresponding images from the respective objects

offering a pragmatic input-output analysis of a huge quantity of information intrinsic to immune function:

(1) Input component: B-cells receive antigen.

(2) Output component: B-cells generate antibody.

(3) Dynamic memory component: B-cells produce antibody referring to immune repertoire.

(4) Hidden units: some recursive B-cells serve simultaneously as input and output units.

This immune network formalism can satisfy Rumelhart and McClelland's (1986) four laws of PDP intelligent computation. In both neuronal and immune networks, the connection is chemical molecules: e.g. neurotransmitters and lymphokines respectively. Both systems can generate an internal cognitive image of the external stimulus (Figure 1), viz. the visual object (in neurosystem) and foreign protein (in immuno-system). Later, classification of future antigenic stimulus occurs by pattern recognition with reference to the memorized image. Nicolis and Prigogine (1977) explored the basis of Jerne's network immunodynamics in terms of non-equilibrium dynamics and stability theory, whereby the immunological configuration can undergo phase-transition, meta-stability and de-stabilization (Perelson, 1988). This angle hints that a tumour system may be immunologically de-stabilized under certain conditions, engendering extinction of the tumour. Our contention of meta-stability and de-stabilization of immuno-dynamic networks appears to be supported by the findings of Mohler *et al.* (1980) and of Mayer *et al.* (1995).

The model we develop for spontaneous tumour regression and progression is an interaction between the anti-cancer agent or immune cell which destroys the malignant cell, i.e. a predator-prey relationship. We can translate this interaction in terms of the standard PDP modes of *Receiving, Storing, Processing and Sending* of information. Here the immune cells (T-lymphocytes and cytotoxic macrophages/natural killer cells) have the following informational modes:

(1) Receiving the informational specifics of a malignant cell by immunologically "hunting" for it.

(2) Storing the information when the immune cell engulfs or attaches to the cancer cell; this is a "resting" state of the immune cell.

(3) Processing the cytolytic information, i.e. digesting or destroying the cancer cell.

(4) Sending information to the immunological network on the lysis of the malignant cell.

**A cybernetic and biothermodynamic foundation of tumour regression**

Classical experimental data of Warburg (1960) and Acs and Straub (1954) indicate that, during carcinogenesis, the energy dissipation, as measured by metabolic activation, increases considerably. We can say that carcinogenesis is a non-equilibrium state as it dissipates higher energy. The normal non-malignant state is a physiological homeostatic state. As per the definition of homeostasis (Zotin, 1990), this normal state is a stationary state with less energy dissipation. Our conclusion is also corroborated by other investigators. Hence we enumerate the reciprocal transformations:

Tumour progression: *Stationary state (non-malignancy) – Non-equilibrium state (malignancy).*

Tumour regression: *Non-equilibrium state (malignancy) — Stationary state (non-malignancy).*

These two complementary processes go on simultaneously, and form a closed cybernetic loop, as detailed later. In the vast majority, Tumour Progression dominates over Regression; whereas in prolonged arrest of cancer, we adduce that Regression is in dynamic balance with Progression. It has been established that cancer onset is a stochastic random but rare mutational process arising usually from a single cell clone (monoclonal origin); the cancer progression can be treated as amplification of fluctuation (Prigogine and Stengers, 1986). Correspondingly, we contend that spontaneous cancer regression can be taken as fluctuation regression. In other words, tumour progression and regression are reciprocal processes, mediated respectively by amplification and regression of fluctuation.

As a system approaches equilibrium or stationary state from non-equilibrium state, the thermodynamic fluctuations of the system gradually relax and reduce; conversely amplification in fluctuations occur during the reverse approach from equilibrium or stationary state to non-equilibrium state. Recall Einstein's formula for Brownian process:

$$p = C \exp (\Delta S/k) \qquad (1)$$

where p is probability density of fluctuation of parameters $U_1, \ldots U_n$ from the equilibrium or stationary values $U^0_1, \ldots\ldots U^0_n$; k is Boltzmann constant and DS is entropy change, i.e. $\Delta S = S - S_0$ (Einstein, 1905). Here $S_0$ is the value of entropy at stationary state. Note that the Einstein equation is the inversion of the Boltzmann entropy equation

$$S = k \log p$$

An equation analogous to Einstein's is derived independently using Markov analysis (Presnov, 1978); using Medawar's formulation that biological development is stochastic. The Brussels and Calcutta schools of nonlinear thermodynamics have extended Einstein's equation (1) to non-equilibrium domain (Glansdorff and Prigogine, 1971; Chakrabarti, 1975). Hence the entropy curvature:

$$p = \exp (\delta^2 S/2k')$$

i.e.

$$\sigma^2 S = 2k' \log p$$

Using some thermodynamic boundary conditions and a Taylor expansion of (dp/dt) around the stationary state, we can show that for this "non-equilibrium state → stationary state" transition (Roy *et al.*, 1999; Zotin, 1990):

$$\Psi = \Psi_0 + [(B.T/p).\ (dp/dt)]$$

and

$$p = p_0[1 - C \exp(-\mu t)]$$

Here $\Psi$ is specific energy dissipation function, $\Psi_0$ is $\Psi$'s value at stationary state, $p_0$ is value of probability at stationary state, T is temperature and C and B are constants. Thence we can derive that (Roy *et al.*, 1999; Zotin, 1990):

$$\Psi = \Psi_0 [1 + A \exp(-\mu t)] \tag{2}$$

which is the Evolution Equation for the Non-equilibrium state → Stationary state transformation. Note that A and $\mu$ are positive numbers. Equation (2) can also be derived through irreversible thermodynamic (de Groot and Mazur, 1967). We now modify equation (2) to describe the reverse transformation: Stationary state → Non-equilibrium state, which is associated with gradual amplification of fluctuation instead of relaxation. In other words, there is a time reversal, which is based on Onsager's stochastic "detailed balance" concept, namely the time reversal invariance of the elementary steps associated with various irreversible phenomena (Onsager, 1968; Nicolis and Prigogine, 1977). Hence for this reverse transformation Stationary state → Non-Equilibrium state, we construct our evolution equation:

$$\Psi = \Psi_0[1 + A \exp(+\mu t)] \tag{3}$$

Note the change of the sign before $\mu$, where $\mu$ is a positive number. Graphs of equations (2) and (3) are shown in Figure 2(a). Transposing equations (2) and (3), we obtain respectively:

$$\Delta\Psi = A\Psi_0 \exp(-\mu t) \tag{4}$$

$$\Delta\Psi = A\Psi_0 \exp(+\mu t) \tag{5}$$

where $\Delta\Psi = \Psi - \Psi_0$, i.e. $\Delta\Psi$ denotes the increase of $\Psi$ over the baseline stationary state value $\Psi_0$. Taking logarithms:

$$\ln[\Delta\Psi] = B - \mu t \tag{6}$$

$$\ln[\Delta\Psi] = B + \mu t \tag{7}$$

where $B = \ln(A\Psi_0)$. In other words, the semilog plot of *ln* $[\Delta\Psi]$ against time *t* would yield straight lines (Figure 2(b)) with negative and positive slopes respectively. Note that, in the two equations, time is measured positively into

the future, and negatively into the past, respectively. Observe that for a biological system, energy dissipation $\psi$ corresponds to metabolic activation, e.g. heat production. We now desire to see whether practical or experimental oncological data corroborate our above-mentioned formalism of Brownian process fluctuation and energy dissipation equations of the tumour progression and regression from a cybernetic perspective.

## Evolution equation of tumour progression and regression

In Figure 3(a) we present experimental data of metabolic activation as described by glycolysis intensity in Ehrich ascites carcinoma; we have used the classic findings of Acs and Straub (1954). The value of Day 5 has been extrapolated from their data. In later days (e.g. Days 9 and 11 ), glycolysis falls due to exhaustion of glycose supply. In Figure 3(b), we construct the lognormal plot of Figure 3(a). Observe the linearity which confirms equation (7). By measuring the intercept and gradient, we can formulate the evolution equation of this Ehrlich carcinoma event.

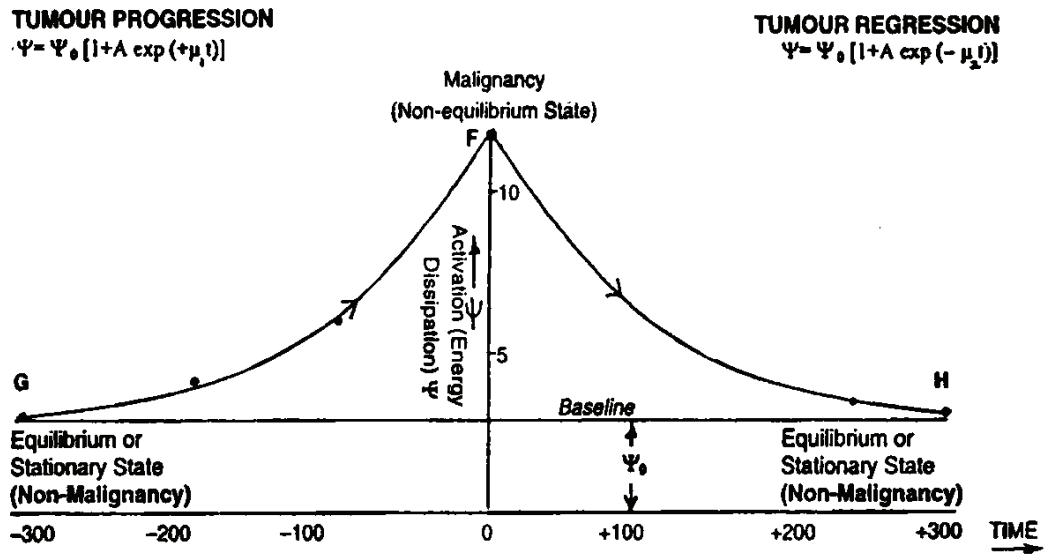



Figure 2a. Cancer progression and regression: schematic representation of exponential hypo-activation and hyper-activation equations (4) and (5). Arbitrary units in axes used. Note changes of sign before $\mu$

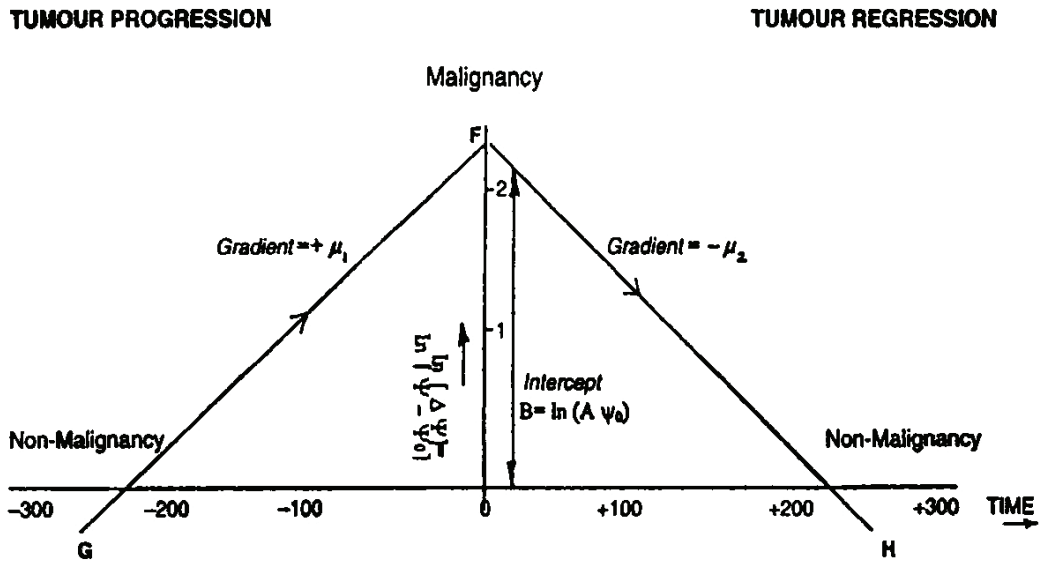



Figure 2b. Schematic lognormal representation of Figure 2a. The parameters $\mu$ and B can be measured as gradient and intercept. Parameter A can be calculated as $B = \ln [A \Psi_0]$ i.e. $A = (\exp B)/\Psi_0$

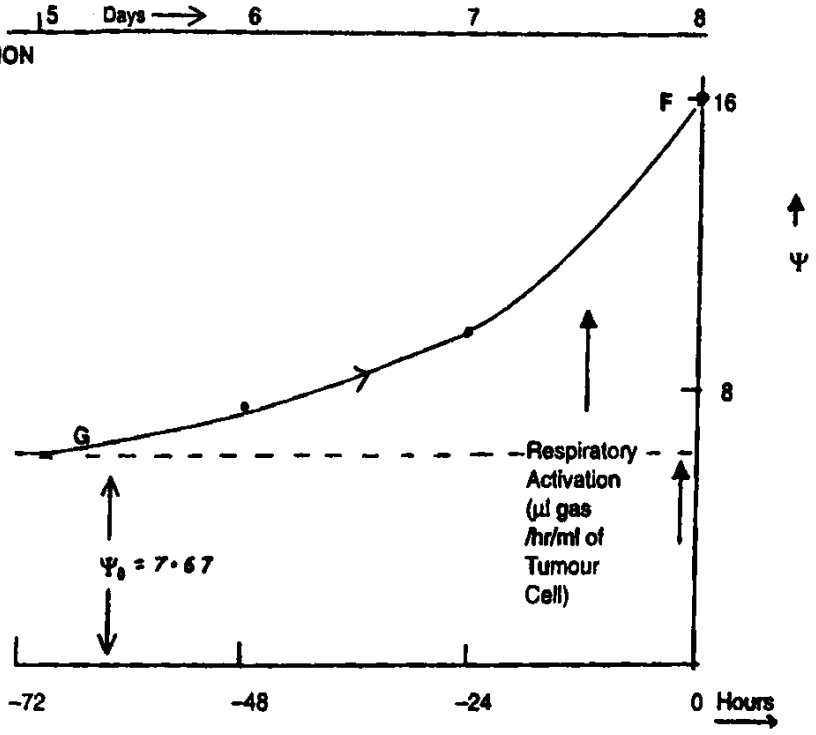
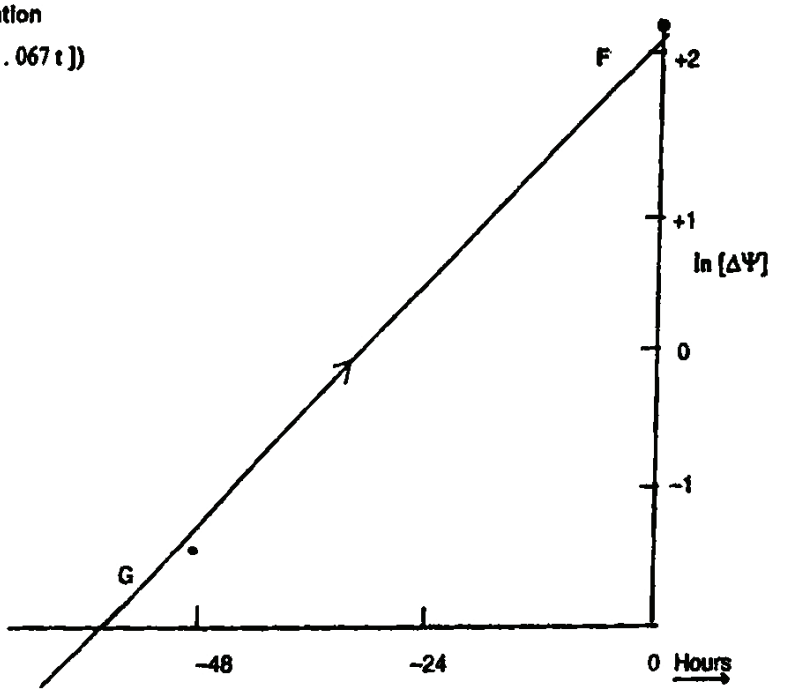



Figure 3a.
Tumour progression: rise in activation or energy dissipation as hr ich ascites arc noma develops

Tumour Progression Equation

$\Psi = 7.67 (1 + 8.026 \exp [+0.067 t])$




gure 3b.
t of ln [$\Psi - \Psi_0$] ai st time '$t$ hil iting linea ity, rc oorating the pli ability of ctu ation form alism d r on-equilib ium rm odynamics to ci ogenesis

Here $\Psi$ is glycolytic intensity in $\mu$l of respiratory gas/hr/ml of cancer cells, and time $t$ in (negative) hours before the peak value F. So note that our mathematical analysis can describe the neoplastic transformation "malignization":

*Hyper-activational transformation*

Benign state ——————————→ Malignant state.

*Amplification of fluctuation*

Figure 4(a) presents a typical pattern of experimental data representing approach to a stationary state as in regression of a lesion (e.g. tumour or wound) or in differentiation during regeneration; we use Vladimirova's (1978) findings. Vertical axis here is drawn to pass through the peak activation point $F_1$. We construct the lognormal plot in Figure 4(b), the linearity confirms equation (6). By measuring gradient and intercept, we obtain the complementary evolution equation

Regression: $\Psi = 100[1 + 3\exp(-0.38\,t)]$

Here $\Psi$ is metabolic activation (estimated as concentration of ATP, adenosine triphosphate, in percent), and time $t$ is in (positive) days after peak state $F_1$. The $\Psi$ scale is a percentage scale, so that ATP concentration at stationary state is defined as 100 percent. Hence our non-equilibrium thermodynamic formalism, based on fluctuation theory and cybernetic approach, appears to describe the neoplastic regression, a process which may be called de-malignization:

*Hypo-activational transformation*

Malignant state ——————————→ Benign state.

*Relaxation of fluctuation*

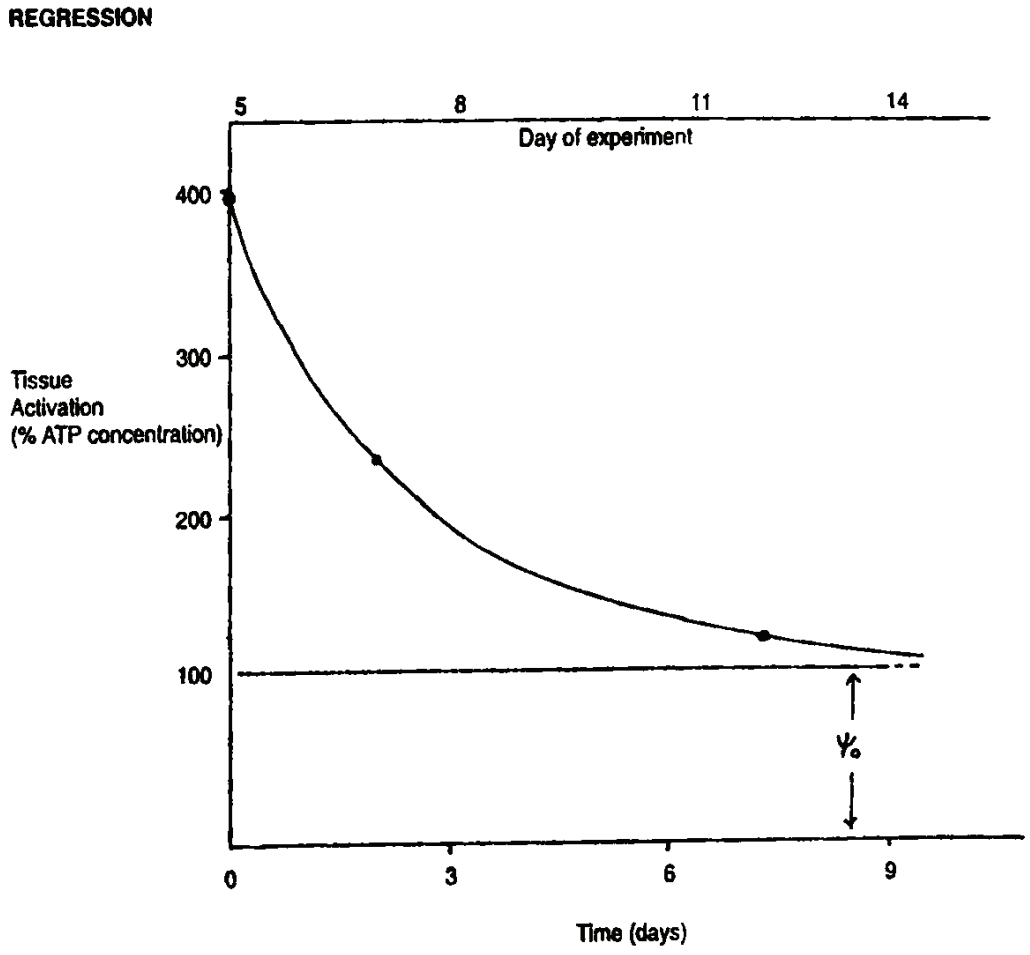



**Figure 4a.** Regression of lesion, e.g. tumour, wound or regeneration. Decrease in activation or dissipation as estimated by glycolysis intensity

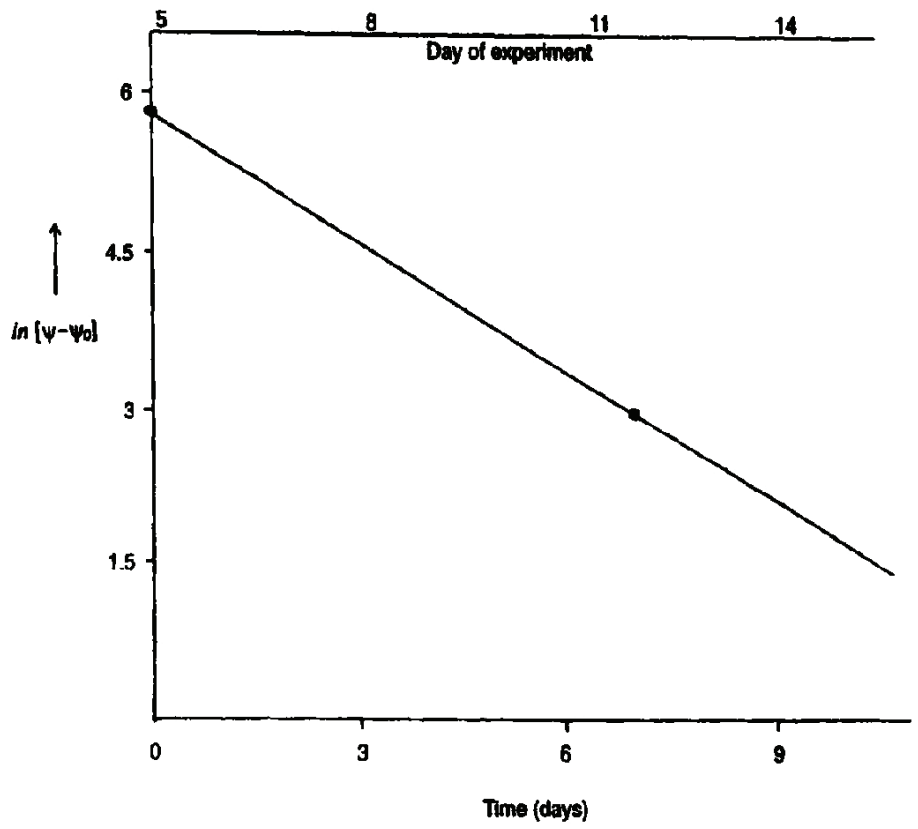



**Figure 4b.**
Plot of $ln\ [\Psi - \Psi_0]$ against time "$t$" exhibits linearity

To conclude this section, we may infer that our non-equilibrium thermodynamic formalism of fluctuation and energy dissipation appears to describe the bi-directional transformations:

Benign state ← → Malignant state.

Our concept of the backward transformation from tumorous condition to normal one, has considerable experimental and theoretical corroboration (National Cancer Insitute, 1976; German Cancer Centre, 1997). In an incisive status report, Shvemberger refers to such a reverse process as "normalization of malignancy" (Shvemberger, 1986). To sum up, our approach elucidates that tumour progression and regression are reciprocal cybernetic processes, mediated respectively by amplification and regression of fluctuation:

Tumour Progression [*Non-equilibrium transformation*] →

Benign state ←——————————→ Malignant state.

← Tumour Regression [Quasi-equilibrium transformation]

**Systems approach to paradoxical self-repair process of spontaneous cancer regression**

Recapitulate that we have earlier discussed Onsager's time reversal complementarity between the two transformations of cancer progression and regression; this complementarity also implies that the reverse transformation of spontaneous cancer regression should be seriously considered by biocybernetic ians. In other words, our biothermodynamic and systems formalism predicts that the reciprocal transformation of spontaneous tumour regression should also occur as a biological phenomenon. In reality, the phenomenology of spontaneous cancer regression is not as uncommon as usually assumed; for example, 24 percent of paediatric neuroblastoma and 30 percent of basalioma spontaneously regresses or arrests subclinically (Kaiser, 1994; O'Regan and Hirschberg, 1993). It is common knowledge that on *post-mortem* examination of motor crash or accident victims, the forensic pathologist observes self-contained cancer foci which have not progressed, such as:

*Self-remission of prostatic carcinoma foci* $\approx$ 35 percent
*Self-remission of cervical carcinoma foci* $\approx$ 60 percent

For two centuries, it has been well-known that there is unexplained episodic tumour remission, spontaneous regression or prolonged arrest of cancer (Kruckenberg, 1889; Rohdenburg, 1918). The therapeutic importance of the causes contributing to the regression, if properly identified, seems very great indeed. The therapeutic promise of spontaneous regression and prolonged arrest is being increasingly emphasized in oncology. Indeed, there have been a number of institutes, programmes and conferences pursuing this problem, such as National Cancer Institute – Bethesda, Maryland; Sonnenberg Klinik, Allensdorf, Germany; Ottawa Cancer Centre, Canada; Centre of Cellular and Molecular Biology – Hyderabad, India; International Institute of Anti-cancer Research, Athens; Helen Dowling Institute – Rotterdam, Institute of Cytology – St Petersburg, University of Sydney; and German Cancer Centre Heidelberg. The potentiality of therapeutic replication of tumour instability or regression is well stressed by Stewart:

> Thinking in the cancer field is perhaps too largely directed to methods of artificial destruction of cancer cell – either by radical removal or its chemical destruction. There has not been enough thought given to the biological control by the host. Of course the former [artificial destruction] is easy when the setting is favourable, and we all lack the courage to undertake the latter [biological control, i.e. spontaneous regression]. Still I am willing to predict that the solution [to the cancer] will be the latter, and that it may not be too many decades away (Stewart, quoted in O'Regan and Hirschberg, 1993).

*Biocybernetic analysis of malignant tumour de-stabilization and regression*

Earlier we have shown the applicability of the fluctuation and energy dissipation formalism to experimental behaviour of tumour progression and regression. Now we explore the oncological application of fluctuation theory further, namely the Wiener model of fluctuation. We have adduced earlier that

fluctuations such as higher temperature are related to tumour de-stabilization. As mentioned before, temperature increases the thermodynamic fluctuations. Furthermore, increased fluctuations can de-stabilize a system as per Glansdorff-Prigogine Theorem. We construct a model of spontaneous tumour regression and progression as a Predator-Prey system. Mathematical study of predator-prey systems by Lotka and Volterra shows that there can be mutual extinction of predator or prey depending on specific conditions. In the case of tumours, the two following cellular species are clear:

(1) *The Predator* is T-lymphocytes and cytotoxic macrophages/natural killer cells of immune system, which attacks, destroys or ingests the tumour cell.

(2) *The Prey* is the tumour cells which are attacked and destroyed by the immune cells.

The Predator has two states, "hunting" and "resting", and destroys the Prey (cancerous cells). Here we follow a biocybernetic approach based on an immuno-dynamic analysis reported by us and others elsewhere (Figure 5(a)) (Roy *et al.*, 1999; Lefever and Horsthemke, 1979). It is easy to see that the tumour progression dynamics, describing the rate of increase of the prey or tumour cell, are:

$$dM/dt = q + [sM(1 - \{M/K\})] - r.f(M) \quad (8)$$

where M is density of tumour cells, "q" is conversion of normal cells to malignant ones (malignant cellular transformation). The term in square brackets is a Fisher logistic growth term implying the increase of tumour cell with replication rate "s" and maximum carrying or packing capacity K. The

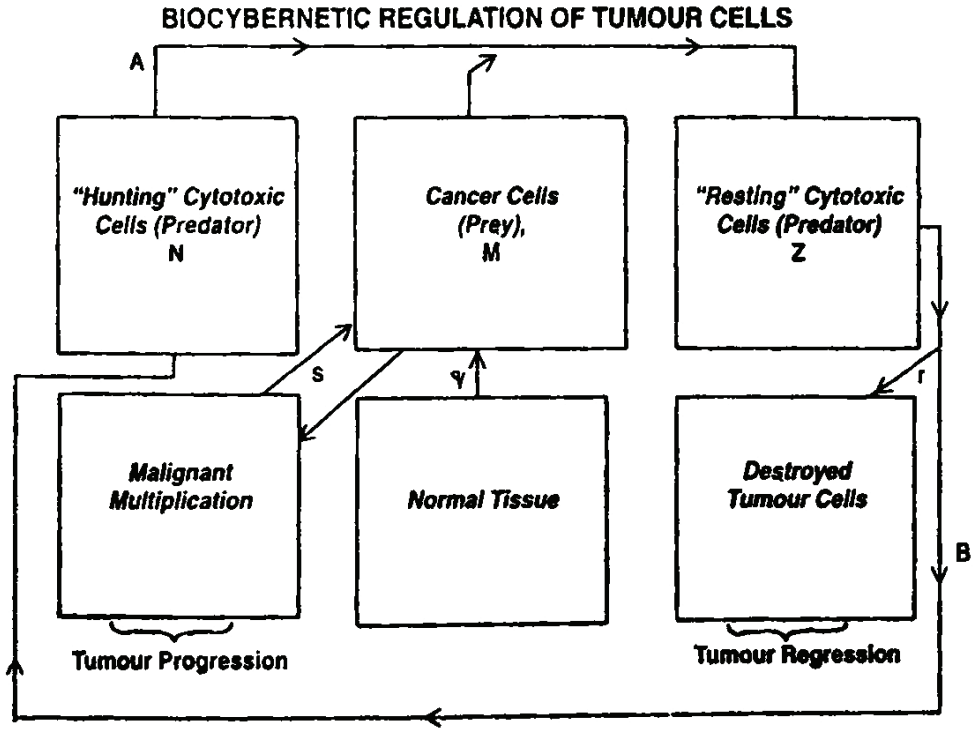



Figure 5a.
Cybernetic regulation of cancer cell population

last term "r.f (M)" denotes that the rate of prey killed (Q) where "r" is rate of tumour cell destruction, and the f(M) is a saturable function of prey density M. In a dimensionless form, equation (8) can be reformulated using re-scaled variables and a re-scaled time $t = (s - q)t$:

$$dm/dt = v + m(1 - um) - r(m/[1 + m]) \quad (9)$$

Steady state solution of equation (9) has a remarkable feature of a cusp catastrophe with instability and critical points at:

$$v' = (1 - u)^3/27u^2\,;\; r' = (1 + 2u)^3/27u^2\,;\; m' = (1 - u)/3u \quad (10)$$

*Wiener fluctuation process and Stochastic Differential Equation (SDE)*

Of special clinical interest to us is "r", the cancer cell destruction rate. We use the standard analysis of stochastic processes and transitions (Horsthemke and Lefever, 1984). Let $r_t$ denote the fluctuation of "r" around a mean value r:

$$r_t = r + \sigma H_t \quad (11)$$

Here $H_t$ is the statistical perturbation with standard deviation $\sigma$. It is clear that for normal cytotoxic or immunological interactions, these fluctuations vary much more rapidly than the macroscopic evolution of the tumour. Then correlation time of the fluctuation can be taken to be zero. Using statistical terminology of the Central Limit Theorem where E denotes the mean expectation value, we have:

$$Er_t = r$$

$$E(r_t - r)(r_t - r) = \sigma^2\delta\,(t - t).$$

Thence, from equation (9) we obtain SDE where $m_t$ denotes perturbation of "m" and $W_t$ the Wiener fluctuation amplitude:

$$dm_t = [v + m(1 - um)r(m/\{1 + m\})]dt + [\sigma m/\{1 + m\}]dW_t \quad (12)$$

that is,

$$dm_t = [F(m)dt] + [G(m)dW_t]$$

where the two terms in square brackets represent the contribution of the deterministic and perturbative process. Let us analyse equation (12) from the standard Ito approach. Treat equation (12) as the continuous limit of a discrete time model:

$$[m_{t+\delta t} - m_t]/\delta t = [v + m_t - u\,m_t^2 - r\,m_t/\{1 + m_t\}] + [m_t/\{1 + m_t\}]\,Q_t \quad (13)$$

Here $Q_t$ indicates Gaussian random nature of variable. Consider steady state solution of equation (12) via the corresponding Fokker-Planck equation focusing on the probability density "p":

$$\partial p(m)/\partial t = -\partial/\partial m[\{v + m(1 - um) - r(m/1 + m)\}p(m)] + [(\sigma^2/2)(\delta^2/\delta m^2)\{(m/1 + m)^2 p(m)\}] \quad (14)$$

The steady state solution of equation (14) is:

$$P(m) = \exp(2/\sigma^2)[-v/m + (v + 2 - u - r)m - (1 - 2u)m^2/2 - um^3/3 + (2v + 1 - r - \sigma^2)ln\, m + \sigma^2 ln(1 + m) \quad (15)$$

We now wish to find the effect of increasing the fluctuation of the tumour cell destruction rate "r", i.e. increasing its $\sigma$, and observe the consequent change of probability P(m). Consider the range of increasing $\sigma$, in the range:

$$0 \leq \sigma \leq 3.$$

Use three representative values of $\sigma$, say 0.5, 0.85 and 2.83, and indicative values of immunodynamic parameters (Lefever and Horsthemke, 1979):

$$u = 0.1;\ r = 5.95;\ v = 2.4.$$

Making these substitutions in equation (15), we obtain the values of the probability density P as the value of tumour cell density "m" ranges from 0 to 6. Thus we arrive at the three curves (Figure 5(b)) for the three values of standard deviation $\sigma$ of the perturbation in the tumour cell destruction rate "r". The cancer cell reduction rate "r" can be fluctuated by perturbing various parameters which influence "r", such as perturbing any of the following parameters:

(1) radiation flux;

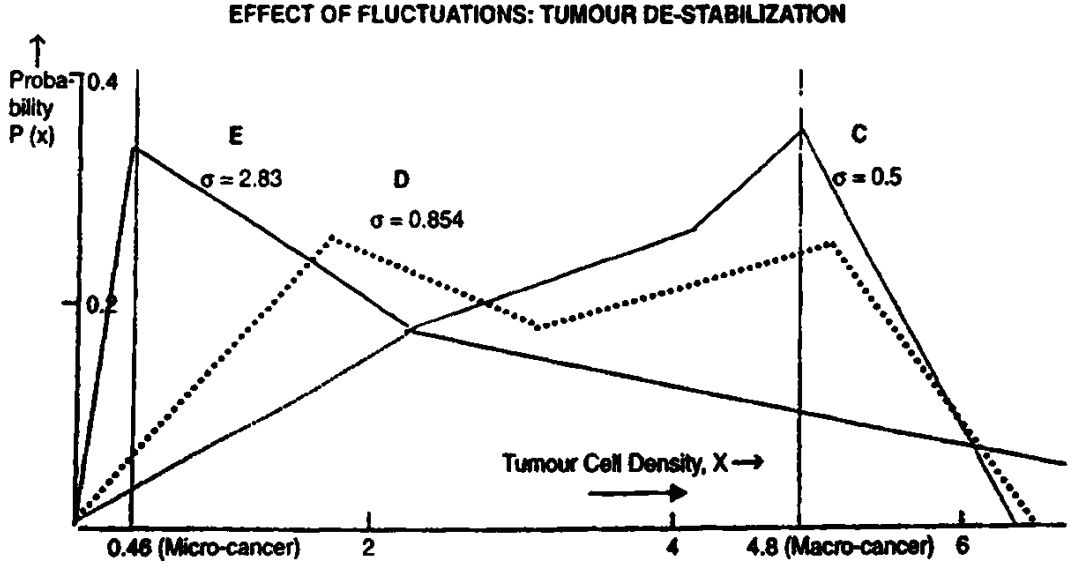



Figure 5b.
Tumour regression and system instability by increasing fluctuations in tumour cells destruction rate $\beta$. Its standard deviation $\sigma$ increases from 0.5 to 0.854 to 2.83; i.e. from C to D to E, whereby the mode value of tumour cell density X decreases from 4.8 (Macro-cancer) to 0.46 (Micro-cancer) enabling regression

(2) cytotoxic chemical flux;
(3) immune cell concentration;
(4) tumour temperature;
(5) glucose level of the blood impinging on the tumour;
(6) oxygen partial pressure, $pO_2$, i.e. oxygenation level in tumour matrix;
(7) haemodynamic perfusion of the tumour, and so on.

*We know that variations in these parameters are reflected as random variations of indices like "r" which give them a stochastic character (Lefever and Horsthemke, 1979).* We see that, as $\sigma$ increases from 0.5 to 0.854 to 2.83, the probability density function P exhibits a non-equilibrium phase transition, apropos the Glansdorff-Prigogine Theorem discussed before. The peak probability density of tumour cells shifts towards very low values of tumour cell density X; for instance, the tumour cell density X shifts from 4.3 ("macro-cancer focus"), to 0.46 ("micro-cancer focus"), i.e. there occurs the *phase transition*:

$$\text{Macro-cancer focus} \xrightarrow[\text{Increase of } \sigma]{} \text{Micro-cancer focus}$$

This corresponds to regression and elimination of malignancy. Hence we infer that if one or more parameters such as oxygenation, radiation or temperature etc. are varied, then the tumour may have a predisposition to regress and destabilize if the standard deviation $\sigma$ of the parameter's variation crosses the following threshold:

*Tumour regression threshold:* $\sigma \leq 2.83$.

We can thus enunciate the corresponding Stability Principle for tumour regression and elimination of malignancy:

> ***General Stability Principle for Tumour Regression:*** *A tumour may have predisposition to de-stabilize and regress if there is a sufficient fluctuation of the malignant cell reduction rate, so that $\sigma$ is 2.83 or above, which may be achieved by correspondingly high variation of temperature, oxygenation, radiation etc.*

*Predominance of cancer cell replication*

The two stages of tumour development were mentioned at the beginning of the last section, namely:

(1) the *initial* malignant transformation of normal cell to the malignant one; and
(2) the *later* process of tumour cell replication where the transformed malignant cell proliferates as a high output process.

In symptom-producing tumour growths, the cancer cell replication (rate "s") proceeds at a considerably greater intensity than the initial event of malignant transformation of normal cells to neoplastic ones (rate "q", density "m"). Hence we can neglect the malignant transformation rate "q" and also rate "v" (which is

proportional to q/s). Thereby eq. (15) reduces to:

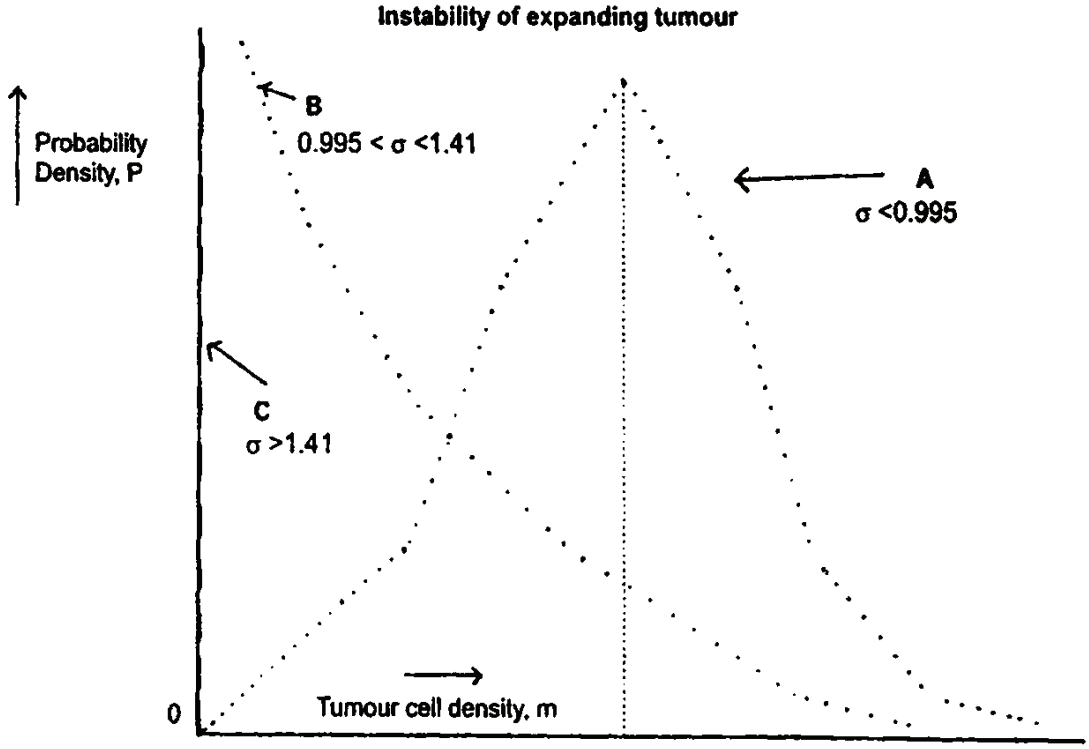
$$P(m) = \exp(2/\sigma^2)[(2 - u - r)m - (1 - 2u)m^2/2 - um^3/3 + (1 - r - \sigma^2)\ln m + \sigma^2 \ln(1 + m) \quad (16)$$

Furthermore the population of the initial malignant transformation cells ("m") is small compared to the tumour cells undergoing rapid replication. Thereby equation (16) approximates to:

$$P(m) = m^{\{[(2/\sigma.\sigma)(1-r)]-2\}} \quad (17)$$

We now explore the behaviour of probability P according to three ranges of $\sigma$ in the variation of "r". In Figure 6(a) we show the behaviour of probability P, adapting the analysis of Lefever and Horsthemke (1979), and plotting the probability with tumour cell density, *vis-à-vis* the $\sigma$ variation. However, in our case we shift our attention to the variation of $\sigma$ while "r" has the indicated value. There are three cases according to the range of $\sigma$ impressed on "r":

Case I: $\sigma < \sqrt{(1 - r)}$. The graph is shown as curve A with a definitive size of the active tumour.




**Note:** Instabilty in an expansive tumour where proliferation due to malignant cellular replication is much greater than initial malignant transformation of normal cells to neoplastic cells. The anti-tumour agent or immune cells is active which produces tumour cell destruction with rate 'r'. The rate 'r' is perturbed with a standard deviation σ. The value of σ is gradually increased. Three types of behaviour are observed with increasing σ:

Curve A – corresponding to definitive size of tumour and malignant activity,
Curve B – corresponding to a smaller tumour activity,
Curve C – corresponding to zero tumour density, implying that the tumour becomes unstable and extinguished.

Figure 6a.

**Case II:** $\sqrt{2(1-r)} > \sigma > \sqrt{(1-r)}$. The situation is denoted by curve B, with the most probable value being $m_0$ the steady point of the Ito stochastic differential equation. The curve tapers towards higher values of "m" where there is also appreciable probability, implying that the tumour population is also active.

**Case III:** $\sigma > \sqrt{2(1-r)}$. The line C illustrates the position, the graph being fully concentrated at zero value of tumour cell population and is reminiscent of a Dirac $\Delta$ function. The line C indicates that the tumour density vanishes and the neoplastic growth becomes extinguished.

In growing tumours, we should consider values of "r" between 0.01 and 1, as per experimental data from Garay (1978). For extinguishing tumours, as a precaution we should always exceed the higher limit of $\sigma$ necessary to de-stabilize the growth. As per the inequality enunciated under Case III, we discern that $\sigma$ is conversely proportional to "r", as there is a minus sign before "r". Therefore it would be prudent to take the lowest value of "r", so that the precautionarily highest value of $\sigma$ threshold could be considered. Perturbations having $\sigma$ value above this threshold would assure tumour de-stabilization. Hence putting "r" = 0.01 in the inequality in Case II, we obtain instability condition in symptomatic proliferating cancer:

$$\sigma > 1.41$$

Hence we may enunciate the threshold condition for regressing the symptomatic tumour:

***Stability Principle for Regression of Symptomatic Tumour:*** *A tumour may predispose to de-stabilize and regress if there is a sufficient fluctuation of the malignant cell reduction rate, so that $\sigma$ is 1.41 or above, which may be achieved by correspondingly high variation of temperature, oxygenation, radiation etc.*

Note the difference with the earlier stability principle. The former principle deals with the situation where malignant transformation of normal cell is to be considered (as in earlier stages), whereas the latter stability principle is concerned with tumours in a later stage where there is much subsequent replication and proliferation of cancer cells. Such tumour de-stabilization may be induced by perturbation of the tumour's temperature, pH, $pO_2$, glucose level etc. (Figure 6(b)). We may mention that perturbation induced de-stabilization of dynamical systems is a well-known concept in biocybernetics and biosystems science. As an instance, using the Langevin approach, one of our collaborators, Robert Kozma, has studied how a system can move from uni-modality (stability) to bi-modality (instability) as base parameter is gradually increased, including a typical clinical de-stabilization process, viz. atrial fibrillation (Roy *et al.*, 2000; Kozma *et al.*, 1996, 1997).

*Kruckenberg Remission Principle and fluctuational aspect of evolutionary origin of cancer*

Our thermal de-stabilization analysis appears to illuminate Kruckenberg's Principle and the evolutionary oncological paradox that aggressiveness and irreversibility of cancer increased with evolutionary progress of animals. Our

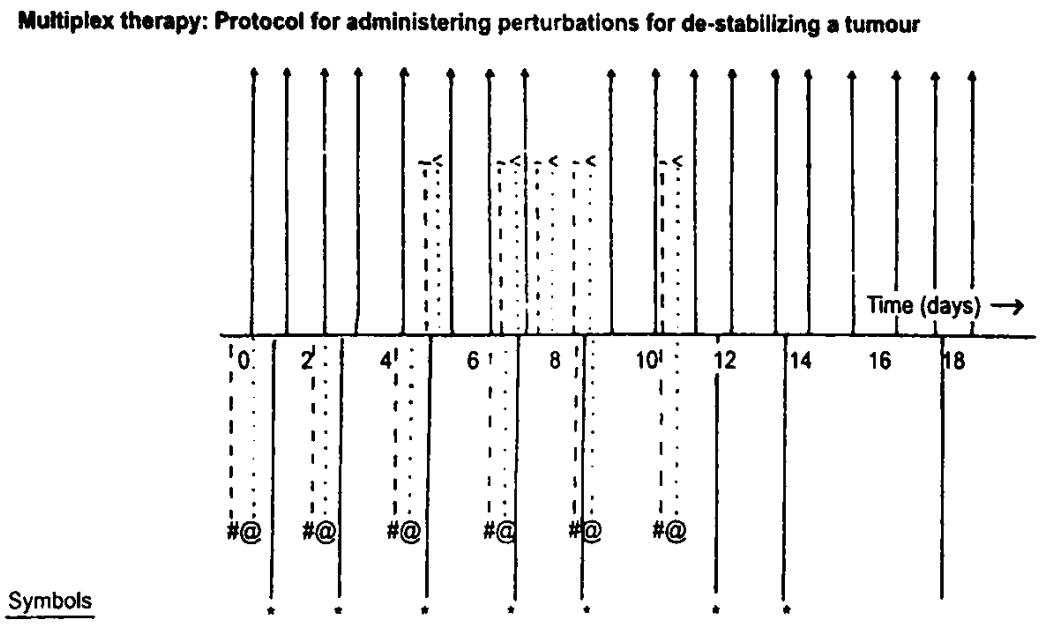



**Figure 6b.**
Multiplicative perturbation therapy: biphasic hyperoxygenation, biphasic hyperthermia, hyperglycaemia, hyperacidosis

formalism appears to furnish a suitable causational clarification of the principle observed by the German gynaecologist A. Kruckenberg (1889), which indicates that the majority of spontaneous regressions of uterine cancer were those associated with induction of high temperature during cautery or curettage of the tumour (Kruckenberg Principle). Furthermore thermal de-stabilization is also applicable to evolutionary oncology. There is high temperature variation of cold-blooded invertebrates reflecting the daily environmental variation of 15°-30°F, whereas for advanced warm-blooded mammals body temperature is nearly constant. So cold-blooded animals might have a predisposition to regress tumours, whereas warm-blooded ones generally cannot. Hence we may elucidate that irreversible malignancy was the price animals had to pay during evolutionary and bio-energetic advancement from heterothermic condition (varying body temperature) to homeothermic condition (constant body temperature). This transition occurred about 250 million years ago; hence we can represent this transition as:

*Aggressive Malignization*

Heterothermicity ——————————→ Homeothermicity

*250 million years ago*

*Experimental confirmation and clinical utilization*

We present experimental confirmation of our model using perturbation of various parameters (Figures 7 and 8). We impart special emphasis to the therapeutic applicability in some of the tumours which are really difficult to treat conventionally.

*Radio-resistant Ewing's bone tumour (temperature variation therapy)*

This tumour is a highly malignant one, and is the only major tumour whose origin still remains elusive or not known with certainty. Our case concerns a 17-year old patient with terminal Ewing sarcoma of left hip. He rapidly went downhill with no response to surgery and 42,200 rads of cobalt-60 radiotherapy with chemotherapy with cyclophosphamide, vincristine and actinomycin-D. As

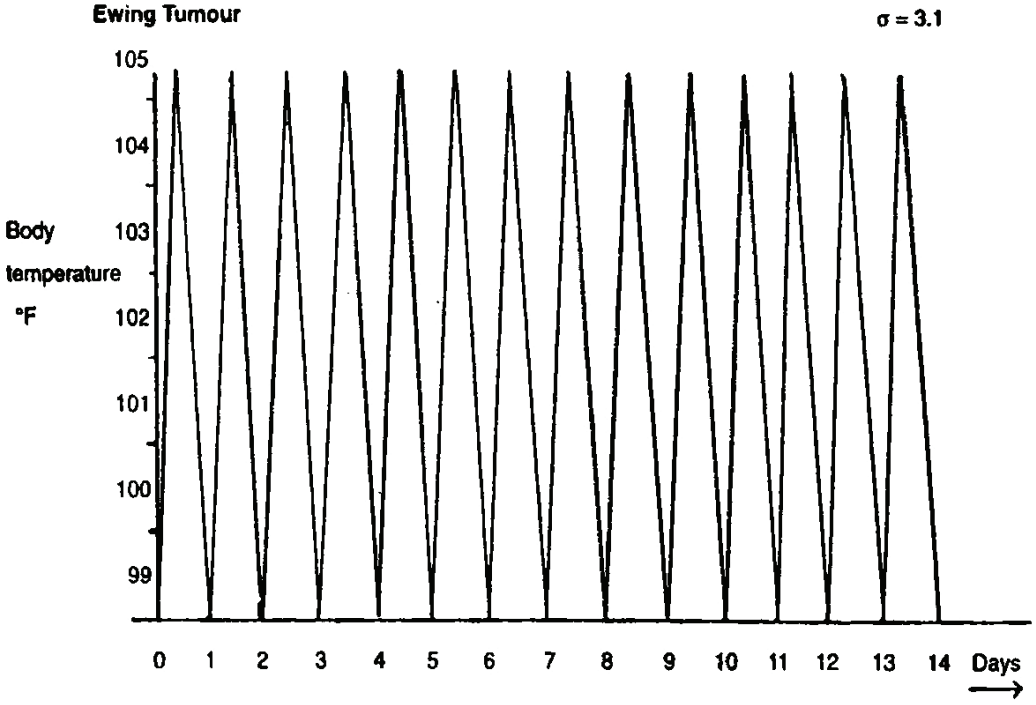



Figure 7a. Complete permanent regression and disappearance of end-stage Ewing tumour of hip after perturbation of temperature. Before the perturbative remission, the patient was deteriorating rapidly without any effect of standard chemotherapy and surgery

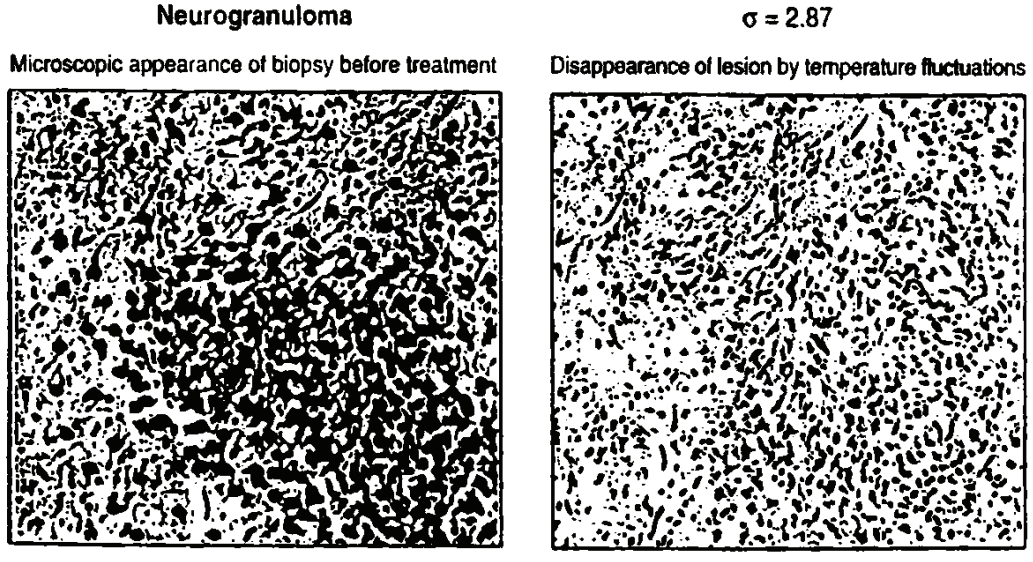



Figure 7b. Regression of otherwise fatal neurogranuloma by perturbative thermotherapy or radiothermia

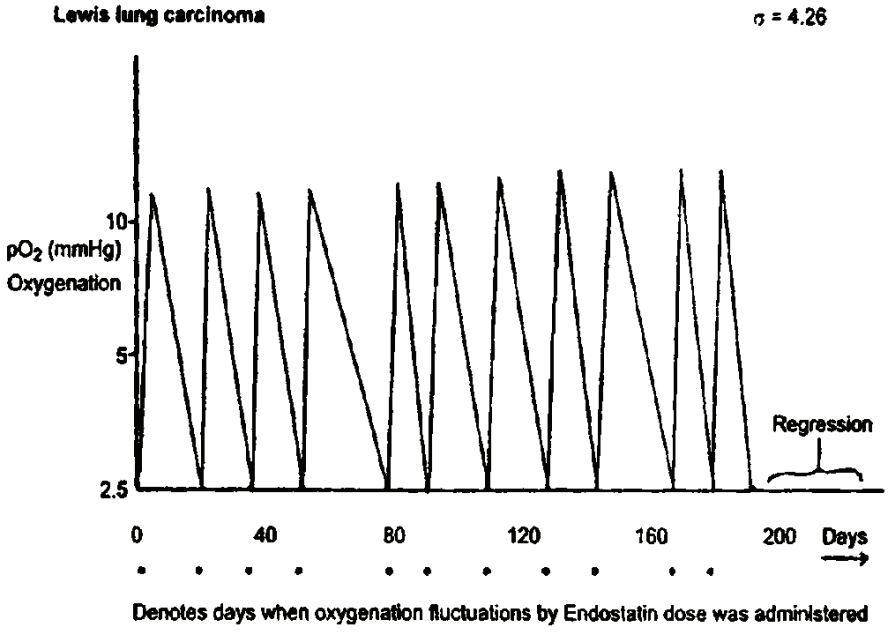



Figure 8a.
Regression of chemotherapy-resistant Lewis lung carcinoma on perturbation of oxygenation i.e. $pO_2$ level using angiogenesis inhibitor endostatin

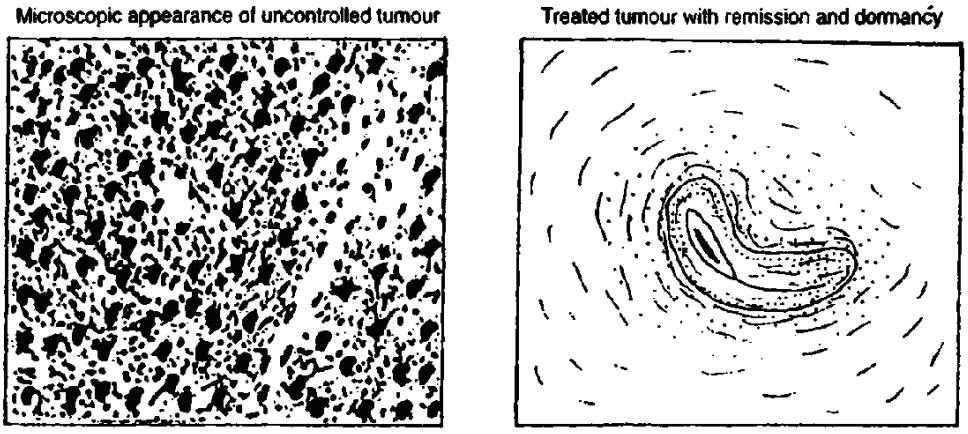



Figure 8b.
Tumour destabilization by means of perturbation of $pO_2$ level using angiostatin. Note the well circumscribed pre-tumour focus, with a fibrotic reaction around the focus which is in permanent dormant state

shown by X-rays, CAT and Technitium-99 scans, he had massive metastasis or spread in chest, mediastinum, spine, skull, ribs and limbs. Later he underwent a prolonged high temperatature fluctuation for a fortnight, with the temperature fluctuating between 99°F and 105°F daily (Figure 7(a)). This was due to a secondary microbial colonisation of surgical site. Temperature fluctuations terminated after anti-microbial therapy. Nevertheless the tumour and metastasis underwent a rapid regression and by two months there was no trace of tumour on CAT and bonescans; the patient lives cancer free today. The case study has been analyzed jointly with our Japanese collaborators of Kanazawa University (Roy *et al.*, 1996). We calculate the $\sigma$ of temperature fluctuation of Figure 7(a) to be as follows which evidently satisfies the tumour regression principle above:

$$\sigma = 3.2$$

*Lung carcinoma (oxygenation variation by endostatin therapy)*
This tumour is one of the neoplasms most difficult to treat by chemotherapy as per the experimental protocol of US National Cancer Institute. This experiment concerns repeated administration of endostatin (a collagen fragment) to young tumours of Lewis lung carcinoma, a very aggressive tumour (Figure 8(a), (b)). Experiments were also successful on fibrosarcoma, melanoma and prostatic carcinoma. Endostatin attacks endothelial cells of new blood vessels serving the tumour and markedly reduces the tumour oxygenation. Six perturbations of endostatin are given at intervals of several weeks causing fluctuation of blood-supply and $pO_2$ level (Roy *et al.*, 1999; Folkman *et al.*, 1997). We find that $pO_2$ of a young tumour is 11mmHg; and during acute oxygen-shortage in a tumour, as with endostatin, $pO_2$ is 2.5 mmHg (average) (Shapot, 1990). Thereby, the tumour, obstinately resistant to chemotherapy, underwent permanent regression. We compute that

$$\sigma = 4.26$$

for the perturbations in Figure 8(a), further corroborating the regression principle. Control experiments were done in two sets of mice, one with saline administered, the other with chemotherapeutic agent cyclophosphamide. Both the sets had rapid cancer progression and died. In the endostatin-treated animals, the tumour regressed and was dormant indefinitely (Figure 8(b)). In other words, there was the experimentally-induced non-equilibrium phase transition:

*Macro-cancer focus* ——————→ *Micro-cancer focus*

Increase of $\sigma$

*Neurogranuloma*
We can regress a lethal trepanomic neurogranuloma mass in the brain (Roy and Sen, 1994; Roy and Biswas, 1996) using fluctuating temperature induced by pharmacological, microbial or physical measures, such as nitro-phenols, mucopolysaccharides, trophozoite micro-organism or radio-frequency diathermy (Figure 7(b)). However, uniform high temperature, instead of a fluctuating one, is considerably less efficient. The latter empirical observation, hinted initially by Wagner-Jauregg of Vienna University in his Nobel Lecture in Medicine, had no rigorous explanation (Wagner-Jauregg, 1927); however, our non-equilibrial model seems to indicate one. Radio-thermia can be induced by a "Selectotherm" equipment using radiofrequencies and robot-controlled spatial scanning apparatus. We observe that the dynamics of neurogranuloma progression and regression can be analyzed by similar biocybernetic principles sketched earlier (Figure 5(a)). Prey is the causative trepanoma organism, and Predator the lymphocytes/giant cells; "q" vanishes as there is no malignant transformation. The anti-neurogranuloma effect of artificially induced thermal fluctuations from 98.4°F to 104°F, appears to be quantitatively accounted for by our analysis. Subsequently temperature spikes are stopped by anti-

trophozoite drugs. One can use trophozoite for producing ten spikes of body temperature fluctuations, one every two days (called "Tertian" periodicity). Our Stability Principle of the immunocybernetics of tumour is satisfied, as we compute:

$$\sigma = 2.87.$$

*Radiotherapy: hyper-fluctuation and hyper-fractionation*

Radiotherapy induces external perturbations and fluctuation of tumour cell reduction parameter "r". Hence our tumour de-stabilization analysis predicts that more efficient tumour regression would be induced by increasing radiotherapeutic perturbations. Our prediction of increase of efficacy of hyper-fluctuation is confirmed by the technique of hyper-fractionation in radio-therapy (Perez and Brady, 1997). Hyper-fractionation and hypo-fractionation are two newer procedures in radiation oncology. In normal fractionation one administers, for example, five exposures/week; in hyper-fractionation one uses two daily exposures (ten exposures/week). On the other side, in hypo-fractionation radiotherapy is administered two days a week, with two exposures in each day (four exposures per week). Typical dose per exposure in hyper-fractionation is 1,200 rads, whereas in hypo-fractionation a typical one is 5,000 rads per exposure. It is found that, considering equal intensity of total radiation dose, there is increased tumour regression by hyper-fractionation than with normo-fractionation. Furthermore, if one decreases the number of perturbations in a week still further by using hypo-fractionation, one reduces efficiency of tumour regression. We present our observation in Figure 9(a). Hyper-fractionation is effective in liver tumour (hepato-cellular carcinoma) and in head and neck cancer – two areas of oncology which are more refractory to treatment.

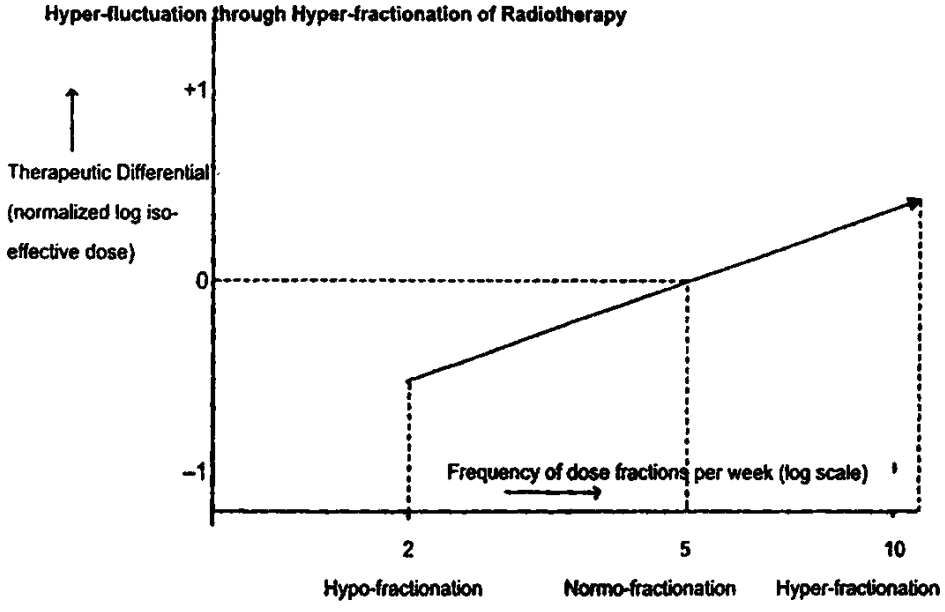



**Figure 9a.**
Increased efficiency of hyper-fluctuation over hypo-fluctuation in radiotherapy. Increased perturbation produces increased anti-tumour effect

*Multiplicative fluctuations as a new multimodality therapy*

Another important type of fluctuation which can produce system de-stabilization is multiplicative fluctuations, combining different fluctuations (Horsthemke and Lefever, 1984). We elucidate that tumour de-stabilization by multiplicative fluctuations is illustrated by the following empirically-observed anti-cancer procedures:

(1) *Multi-step therapy or multiplicative therapy*: Here we can use perturbation in the form of increasing arterial $pO_2$ to 90mmHg, decreasing venous $pO_2$ to 20mmHg, using hyperthermia up to 105°F, hyperglycaemia up to 600mg% blood glucose level, which also produce pH perturbations (up to 6.5 from the normal tissue level of 7.8). Owing to variation of oxygenation, there is perturbation in the oxygen index of the blood $\eta$ as:

$$18.5 < \eta < 42.$$

The treatment is administered daily for two hours for a period of 18 days. In terms of the number of tumour cells destroyed, the technique presents a hundred-fold increase in cell kill. We present Figure 9(b) to illustrate regression of a huge clear cell tumour above the knee with a size of 2Kg. On applying the multiplicative therapy on the patient, the tumour completely regressed and the patient is alive and well five years after regression and there is no sign of the disease. The efficacy of multi-step therapy has also been investigated by von Ardenne, Chaplain and Kruger at the University of Dresden (von Ardenne, 1990a, 1990b). The technique has also been used in mammary cancer, basalioma, melanotic involvement, gastric carcinoma and disseminated metastasis.

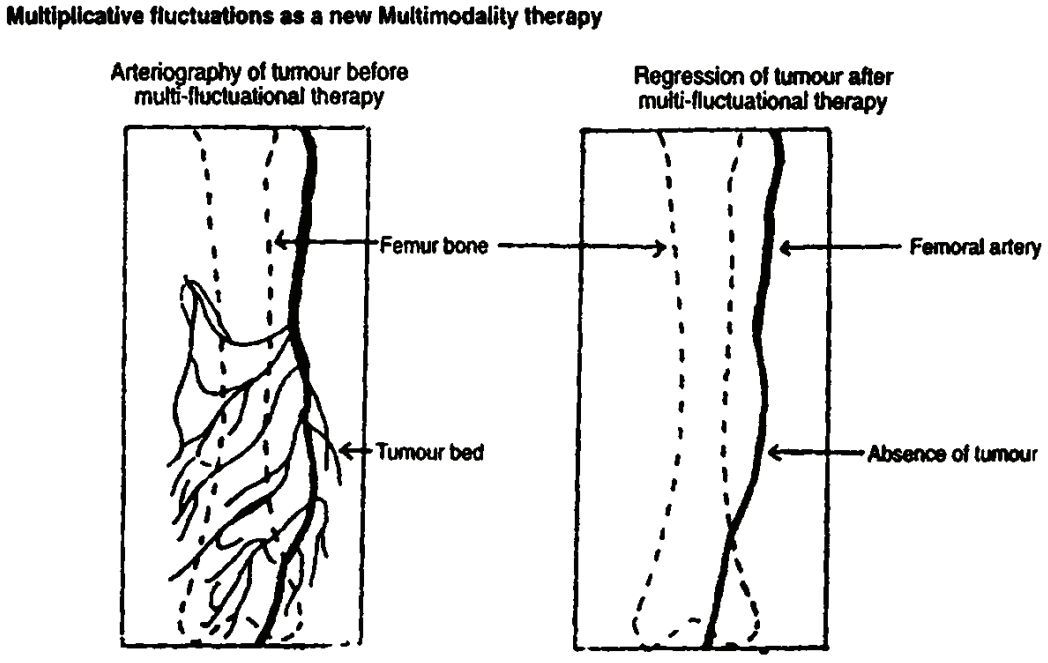



Figure 9b. Effect of multiplicative fluctuations ("multi-step therapy") combining fluctuation of Selecuron radiothermia, hyperoxygenation, radiotherapy and hyperglycaemia using high glucose variation, thereby producing complete regression in severe clear-cell sarcoma near knee

(2) *Multiplex therapy*: Here one uses combined perturbation of glucose level, temperature, anti-tumour drugs, radiation, thermolabilizer, and radiosensitizer (Figure 6(b)). Concentrated glucose solution is administered through superior vena caval catheter and the following perturbations are induced:

(a) *Hyperglycaemia* – Glucose level is varied between 400mg/100 ml blood and normal level of 100mg/100ml blood;

(b) *Hyperthermia* – Temperature variation used is from 98°F to 103°F, using high frequency inductive heating;

(c) *Oxygenation* – administered through pulmonary ventilation.

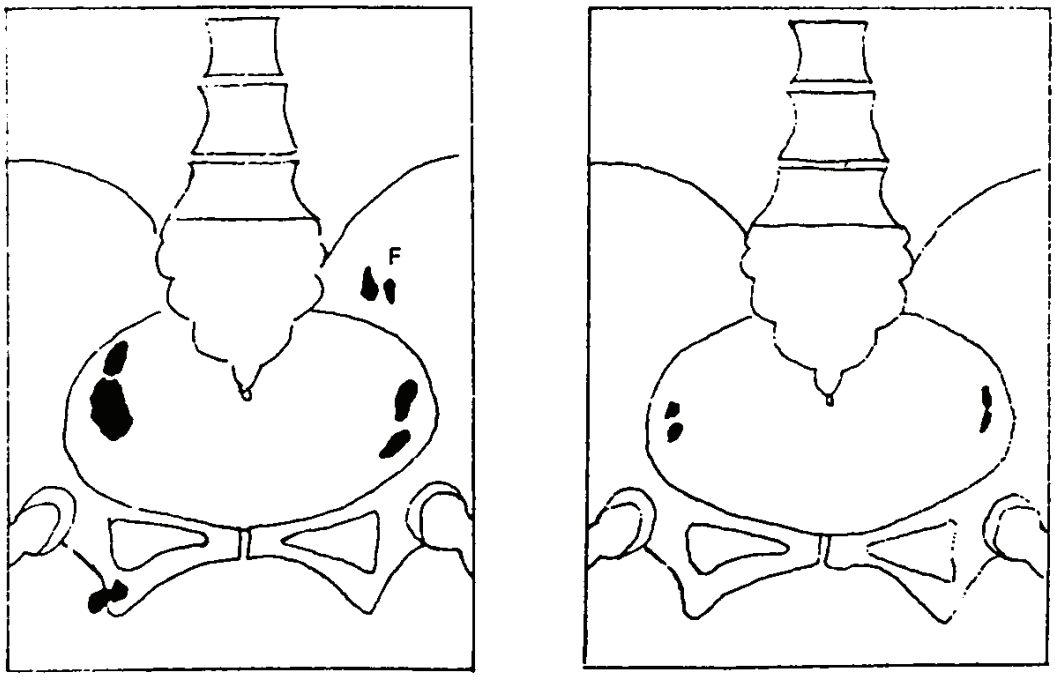
Within a fortnight, the lesions diminish and there is necrosis and apoptosis in the tumour cells which markedly shrink, even if they have been resistant to earlier radiotherapy or chemotherapy (Figure 9(c)). Fradkin, Alexandrov, Savchenko and coworkers at Minsk Cancer Institute have concurrently observed the high efficiency of this multimodal therapy (Fradkin and Zharrid, 1991; Fradkin and Marricher, 1990; Minsk Cancer Institute, 1997). The technique has been used in patients with far advanced incurable cancers, especially in melanoma, chondro-sarcoma, osteo-sarcoma, breast cancer etc.

*Bi-thermia*

We are presently exploring the various multiplicative perturbation modalities to pursue more efficient tumour regression. It may be mentioned that the Dresden and Minsk findings are purely empirical and based on trial and error experiment; nevertheless our formalism of perturbation-induced tumour

Lymphangiographic X-Ray investigation shows metastatic nodal spread in waist

Regression of metastasis after multiplex therapy

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de-stabilization transpires to give a firm theoretical foundation to those approaches. We are devising pH perturbation and "Bi-thermia" which combines hyper-thermia and hypo-thermia. Much higher fluctuations can be obtained safely by temperature variation from 96 F to 102 F with

$$\sigma = 5$$

*Pleiotropicity – malignant generators in cancer cells*

Since our model indicates successively increasing rate of progression with deviation-amplifying feedback, our approach also appears to give a bio-mathematical corroboration of the cytological concept of "pleiotropy", in which changes in a relatively small number of central regulators or cytological control centres are able to elicit a large number of distinct changes in cell phenotype. It is the same mechanism of natural selection of the amplification of fluctuation which favours biological evolution and tumour evolution. Thus the tumour growth and energy metabolism increase. That is, energy metabolism and the non-equilibrium process appear to be a driving force of tumour progression, just as those factors also seem to be the locomotive of the Prigoginian model of biological evolution. Our benignancy → malignancy continuum model may provide a theoretical basis of Foulds' Law of oncology (Foulds, 1980), a most fruitful generalization, indicating that the final tumour has evolved through a phase-wise transition and alteration from the normal benign ancestor.

## Advantages of the newer immunocybernetic approach: promise against therapy resistance

The main handicap of contemporary cancer treatment is drug-resistance, because genetically-unstable cancer cells mutate into drug-resistant ones. However, the earlier examples of our perturbational therapies do not target the genetic mechanism of neoplastic cells *per se*, but work through temperature, $pO_2$ or glucose perturbations which are somatic procedures without genetic interactions. Recently, the great promise of non-genetically targeted treatment has naturally elicit keen interest and the importance of angiostatin therapy can be underscored by the observations of Kerbel (1997), the reviewer and commentator of endostatin's potentiality in the journal *Nature*:

> Nonetheless, we may now have a strategy that has a chance of defeating what has always seemed an inevitable and invincible property of malignant tumours [namely resistance to chemotherapy] ... The results ... could herald a new era of cancer treatment. Perhaps the most significant finding was that all treated tumours eventually become indefinitely dormant even when endostatin treatment was halted. [Regarding] this startling event the basis ... is unknown ...

Our model of perturbation-induced de-stabilization can provide a basis for this "startling event". We use a heuristic approach, modifying the assumptions or techniques to better suit gathered data and patients as our approach evolves.

## Concluding remarks

We have elucidated how the recent developments of immunocybernetics, utilizing tools from synergetics, statistics and nonlinear dynamics seem to open a novel approach to medicine and oncology, through newer physical therapies such as multi-modality perturbational therapies. This appears to be a challenge to physicians and physicists, just as it is to systems scientists and control theorists. Naturally a collective collaborative effort amongst physicians and cyberneticians is imperative if success is to be attained. The paradox of tumours' self-regulation, control and self-repair, viz. spontaneous regression and tumour de-stabilization, and their therapeutic duplication in patients, provides a really substantial promise for patients. Indeed, the remarkable phenomenon of Nature's self-repair of cancer gives a solid hope that, with further research, there is full possibility of complete reversion of malignancy. Possibly biocyberneticians and biosystems analysts have a greater role and responsibility for contribution towards clinical application and human wellbeing in oncology than probably in any other field of biology or human sciences.

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