From Neurocomputation to Immunocomputation—A Model and Algorithm for Fluctuation-Induced Instability and Phase Transition in Biological Systems

Prasun K. Roy, Robert Kozma, and D. Dutta Majumder

***Abstract*—This paper explores bioinformatics-based modeling of immunological instabilities. We develop an algorithm for analyzing stability-instability properties of complex systems and use the developed technique to induce transitions in physical, biological, and engineering systems. As a case study, we analyze the phenomena of tumor destabilization or spontaneous biological regression of a malignant focus-lymphocyte interactive system. Using stochastic noise analysis, we model high-dimensional collective oscillations of nonlinear elements and study nonautonomous systems with oscillation-induced phase transitions between low- and high-dimensional states. The associated nonlinear immunodynamical phenomenon of nonequilibrial destabilization of a malignant tumor is analyzed in terms of Prigogine–Glansdorff stability theorem of dynamical systems theory.**

***Index Terms*—Cancer treatment, immune system, immunocomputation, neurocomputation, nonequilibrium dynamics, stability theory.**

I. Introduction

THE similarity of cooperative behavior of regulation and stability displayed by diverse systems, such as neurological or immunological, is a basic facet of synergetics and cybernetics [1], [14], [24]. Our approach envisages that similar principles of stability–instability transition operate in neurodynamic and immunodynamic systems as they both synergetically comprise the same plan: an emergent collective behavior of individual elements (neurons or immune cells). Despite the fact that neural and immune systems are different structurally, they are comparable functionally, as they deal with same currency, namely, information and control. Reminiscent of the neuronal system, the immune system learns new information, perceives the environment, recalls previously learned information, and makes decisions of action and regulation. The immune system displays the "perception-action cycle" so familiar to neuropsychologists. Indeed the immune system and the neuronal system epitomize the emergent computational action [8] of cybernetic and synergetic behavior.

According to the neurocomputation approach, the intelligence, stability, and regulation of a system is generated by the connectivity between the components, which goes far beyond the properties of individual elements [58]. In the immune system, the cytokine-lymphokine enmeshed pattern forms the interconnectivity [69]. In the 1990s, a new computational field of research has emerged, namely, artificial immune systems (AISs), which link several emerging computational areas inspired by biological behavior, namely, artificial neural networks and artificial life. Dasgupta *et al.* have explored the spectrum of this immunoinformatics approach along with innovative, practical applications [10]. One can construe that the immune system (lymphocyte elements) can behave as an alternative biological model of intelligent machines, in contrast to the conventional model of neural system (neuron elements) (see Fig. 1). In other words, lymphocytes can substitute neurons to model intelligence. Neurocomputation can serve as a tool for the investigation of intelligent immune systems, and offers a realizable input-output analysis of the huge quantity of information processed during immune system functioning.

The considerable potentiality in immunological application for two foundational areas of computer science—namely, cybernetics or systems theory—has been signified by Doherty's pioneering investigations [12] and by Bruni *et al.* [6]. Bruni *et al.*'s investigations have initiated the subject of systems immunodynamics, i.e., the collective behavior of immune system from component cellular elements. Immunodynamics displays self-organization and adaptive information processing, the characteristics of a typical nonequilibrium system. Doherty's 1996 *Nobel Lecture in Medicine* hints at the role that nonlinear dynamics and cybernetic control (homeostasis) plays in immunology [12]. An important area of computational immunodynamics is stability–instability transition, which gives us a computing method to construct an algorithm for investigating stability–instability properties of nonlinear systems in general. The basis of our approach is the Brussels model of nonequilibrium dynamics, which enunciates the following: the Glansdorff–Prigogine (G–P) stability theorem, which states that an open nonlinear system may become unstable at an appreciable distance away from stationary state by means of sufficient nonequilibrium perturbation [22], [26].

Our present study is based on earlier investigations to immunodynamics by Roy and Dutta Majumder [16], [53], [54]. Earlier, Sen and Roy had attempted an analysis of tumor destabiliza-

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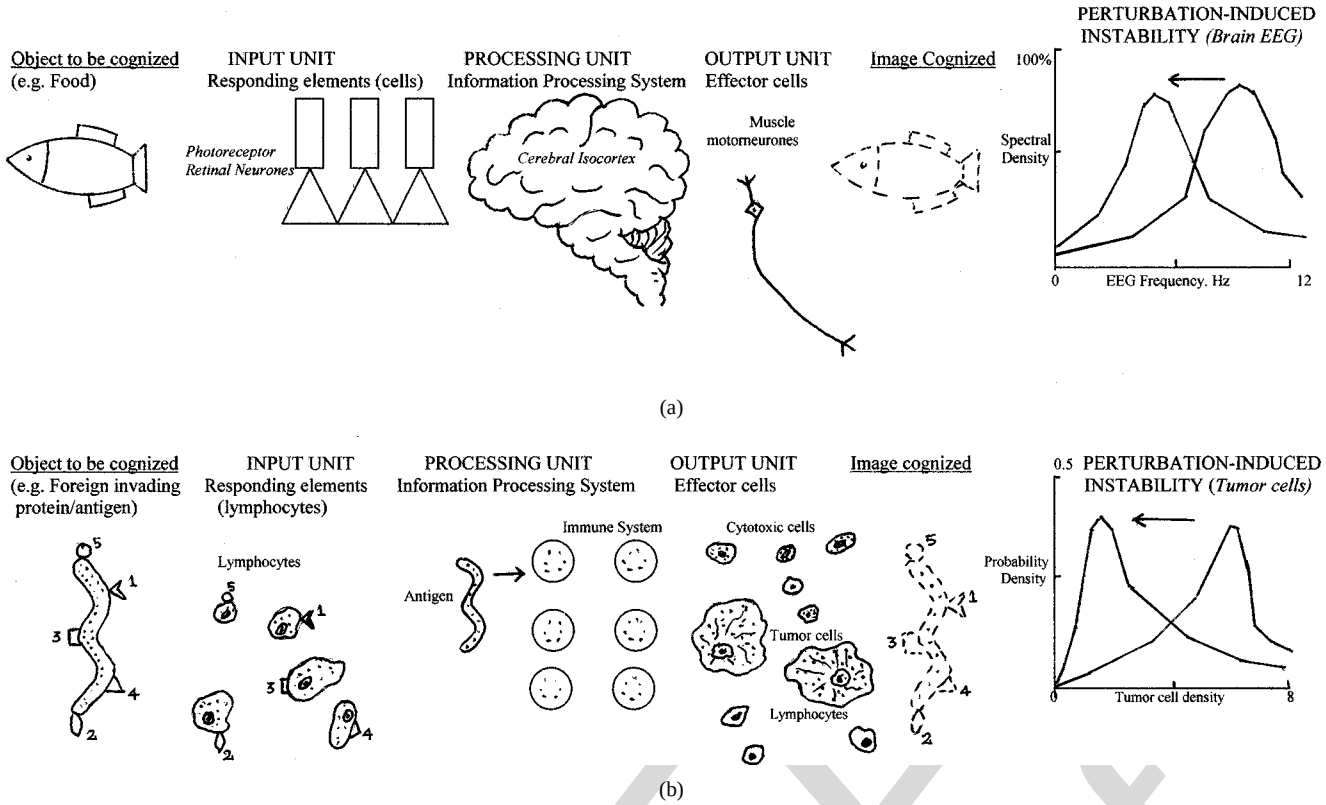

Fig. 1. (a) Neurocomputation and (b) immunocomputation as comparable intelligent processes. Components of the information processing model are displayed for the neurocognition and immunocognition operations through image formation regarding an external object. Graphs on the extreme right show the neural and immune systems undergoing destabilization by induced perturbations: 1) petit mal seizure induced by photic perturbation in the neural system and 2) tumor regression and dormancy induced by temperature perturbation in the immune system.

tion from systems approach perspective [59]. During the 1970s, Dutta Majumder, in the first Norbert Wiener Lecture, developed a unified cybernetic approach to action and self-organization in biological and computational systems [13]–[15]. Phase transitions and collective dynamical behavior in spatially extended physical and biological systems has been studied extensively using models of coupled oscillators [19], [33]–[35]. In the recent Wiener lecture, Prigogine has stressed the new paradigm of nonlinear dynamics and stability in biological systems [49]. One of the present authors has explored the clinical applicability of externally induced immunomodulation on regressing Kaposi tumor on patients [9]. From an immunoinformatics angle, the paper tries to develop a basis of instability of biosystems and harness it for a new method for cancer therapy. We adopt a nonequilibrium approach to tumor progression-regression and a stochastic analysis to tumor instability.

A. System Instability and Phase Transition From an Algorithmic Angle

During recent decades, the disciplines of computational dynamics, nonequilibrium processes, and stability theory have emphasized the importance of small fluctuations that can drastically alter the behavior of systems, whether physical, biological, informational, or engineering systems [26], [41], [48]. Study of such transitions toward instability and metastability is a most fascinating field of engineering and of biomedical sciences. These studies have brought about a more unified vision of the laws that govern self-organization, stability, and instability in complex systems. A major achievement is the notion of phase transitions related to instabilities that occur in open nonlinear systems. Instabilities in nonequilibrium systems have been known from the turn of the century. Examples include the Briggs–Rauscher reaction in chemistry, optical bistability in physics, illuminated photothermal systems in electronics, and genetic selection in biology. Others are the Brusselator and Oregonator "dissipative structures" in autocatalytic biological or chemical systems, as well as Lotka–Volterra interactions in predator–prey systems, host–microbe systems, or grain-locust systems [26]. It is not unnatural to find similar instability phenomena in tumor system as well. The related tumor behavior is called tumor dormancy, prolonged arrest, or spontaneous remission. For instance, autoregression of malignant foci of prostate, uterine cervix, neuroblastoma, and basalioma cases occur as high as 34%, 60%, 23%, and 30%, respectively [29], [44]. Spontaneous regression and very long-term arrest of cancer is a most paradoxical, captivating, and promising phenomenon in immunology [28], [64]. A MEDLINE search (1966–2000) yields 201 723 references to the terms "spontaneous regression" or "spontaneous remission."

The aim of this paper is to study the process of fluctuation-induced transition in immunological system (specifically, the host–tumor immunological system) and thereby develop an algorithm for analysis of system behavior under influence of perturbation or external noise. This algorithm can then be applied to the analysis of instability in other systems from an engineering point of view. This paper is organized in the following

fashion. In Section II, we develop an information-processing approach to immunological systems, with the perspective of the immunological interaction between the host lymphocyte and the tumor cell, the efficiency of which will determine the tumor progression or regression. Section III shows suitability of the nonequilibrium dynamic approach to the tumor system, its reversibility, and the complementarity between tumor progression and regression. In Section IV, we develop a stochastic model for fluctuation-induced instability in tumor immunodynamical system from which we develop a computational algorithm for analyzing stability condition of a general system under perturbation. Section V provides experimental confirmation of the algorithmic approach and show how the tumor immunodynamic system can be destabilized and regressed by perturbation. In Section VI, we delineate a computational algorithm for investigating or predicting instability of engineering system under a perturbative disturbance. In the Appendix, details of the mathematical derivations are introduced.

II. Information Processing in Neural Networks and Immune Systems

Destabilization due to perturbation is an intrinsic feature of complex systems consisting of a large number of interacting elements, such as the neural system or the immune system [see Fig. 1(a)]. For the neural system, the classic example is how flashing lights (photic perturbation) on some patients may destabilize their ordinary neural state (having EEG α wave of 9–11 Hz), induce petit mal seizure (EEG 4–5 Hz). Perturbation-induced instability can also occur in the immune system. For example, sufficient temperature perturbations might destabilize the host–tumor immunodynamic system, leading to tumor remission. Accordingly, tumor density may shift from high to low concentration. Using this interrelation of neural and immune instability, we analyze stability issues in immune system. Insight into dynamics of tumor remission is obtained by modeling high-dimensional collective oscillations in a population of nonlinear elements and studying nonautonomous systems with oscillation-induced phase transitions between low- and high-dimensional states.

The last decade has witnessed extensive investigations on the role of lymphocytes in tumor instability and spontaneous cancer regression [11], [25], [38], [40], [69]. We establish a model of immunodynamic instability and spontaneous tumor regression and progression from an information processing perspective, in terms of *reception*, *storage*, *processing*, and *transmission*. During the working–resting cycle of the lymphocytes, the immune cells or lymphocytes have two alternating functional phases: active (A) and passive (P) phase, respectively. The actual phase A or P depends on whether the lymphocyte is in the working mode (hunting or counteracting the tumor cell) or in the resting mode (recuperating state after the tumor cell has been counteracted). Each mode consists of two of the informational operations, and these cyclically repeat as further new tumor cells are presented to the lymphocyte.

Active mode (A-mode):

1) *Reception:* The lymphocyte receives information when it accesses or pursues for the malignant cell.
2) *Storage:* The lymphocyte stores the accessed information when it attaches to or engulfs the tumor.

Passive mode (P-mode):

1) *Processing:* The lymphocyte processes the information of the assimilated cancer cell.
2) *Transmission:* The lymphocyte transmits the processed information to the immune system.

If the duration of the active and passive phases are t' and t'', the rate constants of the two phases are $k_1 = 1/t'$ and $k_2 = 1/t''$, respectively. Indicative values of k_1 and k_2 for cytotoxic immune lymphocytes are 0.43 and 0.85 per day [62], whence $t' = 2.35$ and $t'' = 1.18$ days, the total duration of active-passive cycle sums to about 3.5 days. There are empirical instances of how the two phases occur. For example, [21], the lymphocytes migrate to the cancerous tissue and interact with tumor cells (active phase). After counteracting the tumor cells, the lymphocytes become quiescent and reenter the passive circulation and the circulatory compartments as the lymph fluid (passive phase). The lymphocyte's longevity is about 100–300 days [21]; thus, there can be many active–passive cycles of 3.5 days.

There is bioinformational corroboration of the two phases of a lymphocyte cell: active and passive. Szent-Gyorgyi's investigation [63] confirms the existence of two modes in a cell: α state, characterized by an excited aggressive invigorated state of nonequilibrium, and β state, described as quiescent recuperative steady state of equilibrium. The two modes of the cell, active/nonequilibrium and passive/equilibrium, is also a basic tenet of bioenergetics [41]. Becker's analysis [4] of biological information processing and signal transmission shows the occurrence of the two modes, which he calls analog (repairing mode) and digital (steady mode). Fluctuations in the amount and type of the immunomodulators as lymphokines occur in the immune reactions and this chemical modulation considerably increases system complexity [69]. Both the neural system and immune system can generate and classify an internal cognitive image of the external stimulus, namely, the visual object (in neural system) and foreign tumor protein (in immune system) (see Fig. 1). Later, classification of future antigenic stimulus occurs by pattern recognition with reference to the memorized image.

III. Information Metabolism—A Biological Information Processing Approach

We study how the nonequilibrium model of dynamical systems can describe the information processing aspects of tumor progression and regression. In this section, the nonequilibrium model is applied to the malignant cell-lymphocyte interactive system. We explore the mathematical and informational basis of the critical concept of tumor reversibility and especially the significance of the delicate reverse transition, namely, tumor regression.

A. Outline of the Analyzed Transitions

In nonequilibrium dynamics, the important characteristic of system activity is entropy production or energy dissipation [41],

[71]. A link between energy dissipation and information processing is provided by the concept of information metabolism and informational dissipative structures [3], [32]. Information metabolism is a biological model based on the structural organization and metabolism of the cells and describes biological information processing in analogy to energy metabolism. Indeed, the this notion of information processing or information metabolism of a biosystem from the computational point of view happens to be the counterpart of the energy dissipation concept of a system from the thermodynamic point of view. Classical experimental data indicates that during carcinogenesis, the energy dissipation, which is a characteristic of entropy production, increases considerably [71], [60]. In other words, carcinogenesis is a nonequilibrium state producing a high amount of energy and information processing. The normal nonmalignant state, being a physiological homeostatic state, is a stationary state with the least energy dissipation or information processing. Hence, we enumerate the transformations.

The two complimentary processes go on simultaneously and it forms a closed immunocybernetic loop. In the greater majority of instances, tumor progression dominates over regression, whereas in prolonged arrest cases, the regression is in dynamic balance with progression, while in spontaneous remission, the regression exceeds progression. It has been established that cancer onset is a stochastic immunogenetic process arising from a single cell clone (monoclonal origin); the cancer progression can be treated as amplification of stochastic fluctuation [50]. Correspondingly, we note that spontaneous biological or immunological regression of cancer can be taken as fluctuation regression. In other words, tumor progression and regression are complementary processes, mediated respectively by amplification and regression of fluctuation. We now proceed to develop a quantitative analysis.

B. Dynamics of Metabolic Information Processing

Let us start with the information-theoretic analysis of the fluctuation processes associated with immunodynamics. We begin with Einstein's stochastic fluctuation equation that describes the relationship between the entropy change and the corresponding probability of stochastic fluctuations as [17]

$$p = C\exp(\Delta S/k). \tag{1}$$

The value of k is $(1/\ln 2)$ or 1.38×10^{-23}, if entropy is respectively expressed in bits or in joules per kelvin [66]. One can extend the latter equation to nonequilibrium domain. We consider the "equilibrium or stationary state $\rightarrow$ nonequilibrium state" transformation characterizing tumor progression (see Table I). This transformation is associated with increase or amplification of the fluctuations. From fluctuation theory and nonequilibrium dynamic principles [7], [22], it is known that the value of metabolic activation of a system at nonequilibrium state (ψ) and at equilibrium or stationary state (ψ_0) satisfies

$$\psi = \psi_0 + (k'/p)(dp/dt) \tag{2}$$

where $k' = kT/V, T =$ temperature, and $V =$ volume. Using Taylor expansion and the corresponding boundary conditions,

TABLE I—**AUTHOR, PLEASE SUBMIT TABLE I**
CLASSIFICATION OF TUMOR TRANSITIONS.

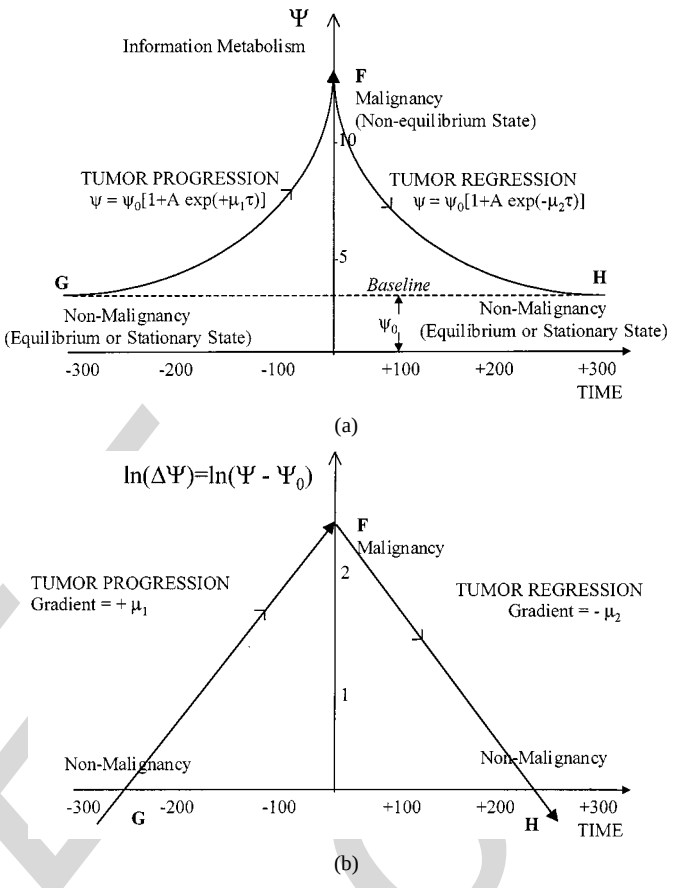

Fig. 2. Schematic information processing approach to tumor dynamics of cancer progression–regression. (a) Increasing and decreasing metabolism calculated according to (4) and (5) during spontaneous progression and regression of malignancy respectively. (b) Semi-log plot of data shown in (a), namely, (5) and (6). Parameters B and μ can be estimated from the intercept and gradient.

the following relationship can be derived for the "Equilibrium state $\rightarrow$ Nonequilibrium state" transition [56], [70]:

Immunodynamic tumor progression

$$\psi = \psi_0[1 + A\exp(+\mu_1 t)]. \tag{3}$$

Here, μ_1 is the tumor progression coefficient, which is a positive quantity. As a next step, we modify (3) to describe the reverse transformation of tumor regression associated with gradual relaxation of fluctuation instead of amplification. 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 [45]. Hence, for the reverse transformation, we construct

Immunodynamic tumor regression

$$\psi = \psi_0[1 + A\exp(-\mu_1 t)]. \tag{4}$$

Observe the change of the sign before μ and that we have used a different suffix (μ_2) to indicate that the rates of progression (μ_1) and regression (μ_2) may not be equal. Note that A, μ_1, and μ_2

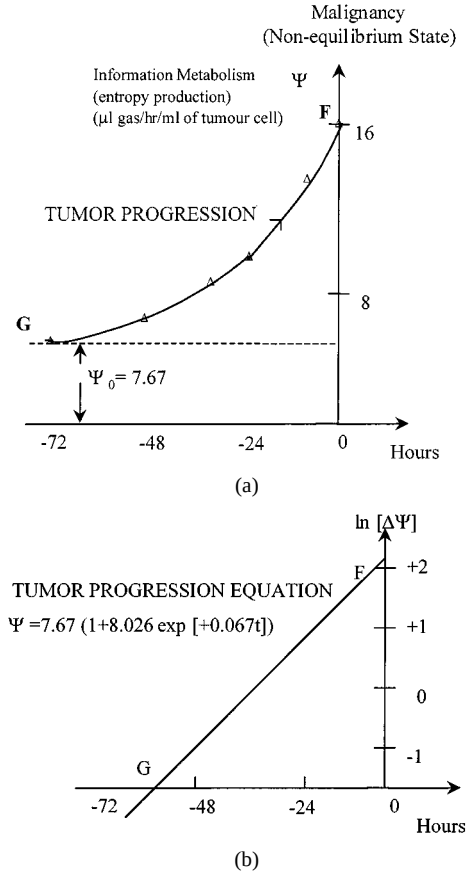

Fig. 3. Experimental data of Ehrlich ascites carcioma advancement. (a) Tumor progression indicates rise in information processing rate. (b) Semi-log plot of the data shown in (a) demonstrating the applicability of the immunoinformatics model.

are positive numbers. The graphs of (3) and (4) are shown in Fig. 2(a). Transposing (3) and (4) and taking logarithms, we obtain

$$\ln[\Delta\psi] = B + \mu_1 t \tag{5}$$

$$\ln[\Delta\psi] = B - \mu_2 t \tag{6}$$

where $B = \ln(A\psi_0)$ and $\Delta\psi = \psi - \psi_0$. Hence, a log-normal plot of $\ln[\Delta\psi]$ against time t would yield straight lines [see Fig. 2(b)] with slopes positive and negative, respectively. Note that in the last two equations, time t is measured positively into the future [right-hand side of Fig. 2(a)], and negatively into the past [left-hand side of Fig. 2(a)]. Observe that the Prigoginian concept of entropy production or energy dissipation ψ corresponds to metabolic activation or information metabolism of the biological system. Now let us investigate equations (3) and (4) experimentally.

C. Experimental Evidence on Information Processing During Tumor Progression and Regression

1) Example of Tumor Progression: In Fig. 3(a), we present experimental data of information metabolism intensity in Ehrlich ascites carcinoma [16]. The value of Day 5 has been extrapolated from the experiments; in later days (e.g., Days 9 and 11), the glycolysis and metabolism falls due to exhaution of glucose supply. In Fig. 3(b), we construct the lognormal plot. Observe the linearity, which is in accordance with (6). By evaluating the gradient, we can formulate the evolution equation of this Ehrlich carcinoma event of tumor progression

$$\psi(\text{Gb}) = 213[1 + 8.026\exp(+0.067t)]. \tag{7}$$

Here, ψ is information processing rate, measured in unit of gigabits per second per gram of tumor cells (1 Gbit $= 10^9$ bits) and time t is in (negative) hours before peak value F. Actually, the raw experimental data is estimated as entropy production or metabolic activation, measured in microliters (μl) of oxygen consumed/hour for every gram (or cm^3) of tumor cells. It is known that metabolic activation of $1\mu l$ O_2 consumed $=$ 0.02016 J of energy dissipation or entropy production. The entropic expenditure associated with processing 1 bit of information output is "$kT\ln 2$," where k is Boltzmann constant and T is absolute temperature. For ambient temperature of 27 °C of the organizm (i.e., $T = 300$ °K), the value of "$kT\cdot\ln\cdot 2$" works out to be 2×10^{-21} J. Thus, 1 J corresponds to 5×10^8 Tb, so that metabolic activation of $1\mu l$ oxygen consumed $= 100.8$ Tb. Using this translation factor, we transform metabolic activation (O_2) into information processing (gigabits). Note that such large information processing levels is intrinsic to biological systems, e.g., total DNA of a human individual has about 10^{22} bits of information [66].

2) Example of Regression: Fig. 4(a), presents a typical pattern of informational metabolism, representing the approach of the system to a stationary state as in regression of a lesion (e.g., tumor or wound) or in repair during regeneration. Experimental data is used [54] and we have used the above-mentioned transformation factor. Vertical axis is drawn to pass through the peak activation point F_1. We construct the log-normal plot in Fig. 4(b), the linearity confirms (7). From simple measurement, we obtain the equation for remission

$$\psi(\text{Gb}) = 946[1 + 0.41\exp(-0.0083t)]. \tag{8}$$

Here, time t is measured positively. Note that the concept of *demalignization* or tumor regression, namely, the "backward transformation" of the immunological system from tumor condition to normal one, has considerable experimental and theoretical confirmation [25], [40], [61]. To sum up, our immunoinformatics approach elucidates that tumor progression and regression are reciprocal cybernetic processes, mediated by amplification and regression of fluctuation, respectively, as shown at the bottom of the page. The mathematical analysis and its experimental confirmation (Figs. 2–4) are applicable under standard conditions. However, in certain clinical conditions, the results might resemble the theoretical equations with less accuracy and the progression curve may show a minor plateau after a major period of exponential increase of Fig. 2(a). This can be due to exhaustion of nutrition, oxygen, glucose, or blood supply and accumulation of toxic or inhibitory metabolites, etc. Moreover, our analysis is applicable to tumors consisting of actively metabolizing cellular protoplasm. Nevertheless, a small number of tumors involve low-metabolizing entities, such as pigment (in melanoma tumor), fat (in liposarcoma), or bone (osteoclastoma). In that case, the curve would exhibit a gradient less that exponential. Notwithstanding, our general approach to progression-regression and reversibility would be applicable. We now

test an approach to tumor instability and G-P theorem when a tumor can be regressed by perturbing its patho-physiological parameters, following the paradigm of nonlinear dynamics and phase transitions.

IV. Immunomodeling of System Instability

In the previous section, the biological relevance of perturbation-induced immunodynamical instability of the tumor has been outlined. In the following analysis, we apply a stochastic model of instabilities in order to describe the behavior of the fluctuations and possible phase transitions. Futhermore, we outline an algorithmic approach with a view toward practical applications for investigating destabilization of complex systems.

A. A and P Phases or the α and β Informational Modes of Lymphocyte

Preliminary studies to immunomodeling have been introduced in [55] and [57]. Now we concentrate at the description of active and passive phases of the lymphocytes, corresponding to α and β modes of information processing of the lymphocyte as described before [see Fig. 5(a)]. Consider the interaction between the lymphocyte and the tumor cell. From Section II, recollect that the duration of the active A phase and passive P phase of the lymphocyte is t' and t'' and the rate constants of the predating and resting phases are $k_1 = 1/t'$ and $k_2 = 1/t''$, respectively. Denote M and N as, respectively, the density of tumor cells and that of cytotoxic lymphocytes in A phase. The intensity Q of tumor cells undergoing processing and extinction by lymphocytes is

$$Q = -(MN)k_1 = -(MN)/t' \tag{9}$$

where MN is the product of tumor cell and lymphocyte densities. The product signifies the intensity of the lymphocyte-tumor cell encounter. The MN product is multiplied by the predating rate constant k_1 of lymphocytes in A phase. The minus sign means extinction or subtraction of the tumor cells. The rate of increase of the predating lymphocytes in A phase is

$$dN/dt = -MN/t' + Z/t'' \tag{10}$$

where the first term $(-MN/t')$ denotes the reduction of the A-phase lymphocytes due to combining with tumor cells [see (9)]. The second term (Z/t'') denotes the generation of A-phase lymphocytes from the P-phase lymphocytes whose density is Z and where generation rate constant k_2 is $1/t''$. In other words, Z should be multiplied by the generation rate constant $(k_2 = 1/t'')$ to give the requisite A-phase lymphocyte generation term. The rate of increase of tumor cells, as per the tumor progression dynamics of Fig. 5(a), is

$$dM/dt = q + [sM(1 - \{M/K\})] - r \cdot f(M) \tag{11}$$

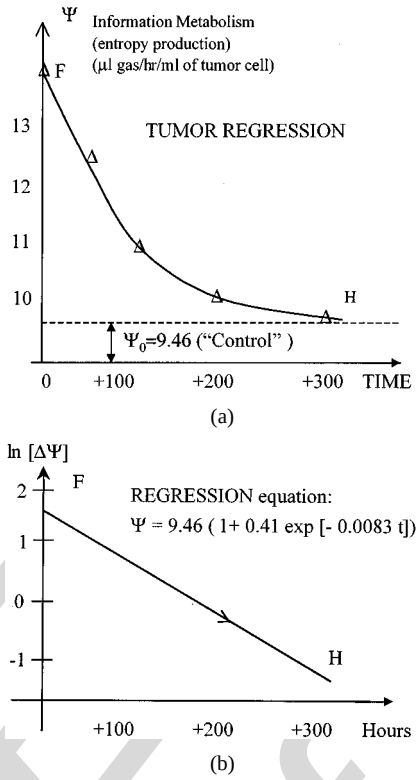

Fig. 4. Experimental data of spontaneous regression. (a) Remission signifies decrease of information processing rate. (b) Semi-log plot approximates linear behavior, supporting the immunocybernetic approach.

where M is density of tumor cells and 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 tumor cell with replication rate s and maximum carrying capacity or packing capacity K. The last term $r \cdot f(M)$ denotes intensity of tumor cells killed (Q), where r is rate of tumor cell destruction and the $f(M)$ is a saturating function of tumor cell population M. Hence, we can use for $rf(M)$ the value of Q in (9). Using (12) and the A and P phases of the immunoinformatics model [see (9) and (11)], we obtain the following dimensionless equation of the scaled tumor cell density m in terms of the corresponding rescaled variables and rescaled time $t = t(s - q)$ (see the Appendix for details):

$$dm = \{v + m(1 - um) - r(m/[1 + m])\}\, dt \tag{12}$$

where $v = qt''/st', u = t'/Kt'', m = M \cdot t''/t',$ and $r = (M + Z)/st'$. The steady-state solution of (12) exhibits a remarkable feature of bistability, i.e., a cusp catastrophe with critical points v', r', m'.

B. Modeling the Perturbation of the Immune System

Since the fluctuation of tissue environment and the stochastic nature of the immune system has crucial effect on the immuno-

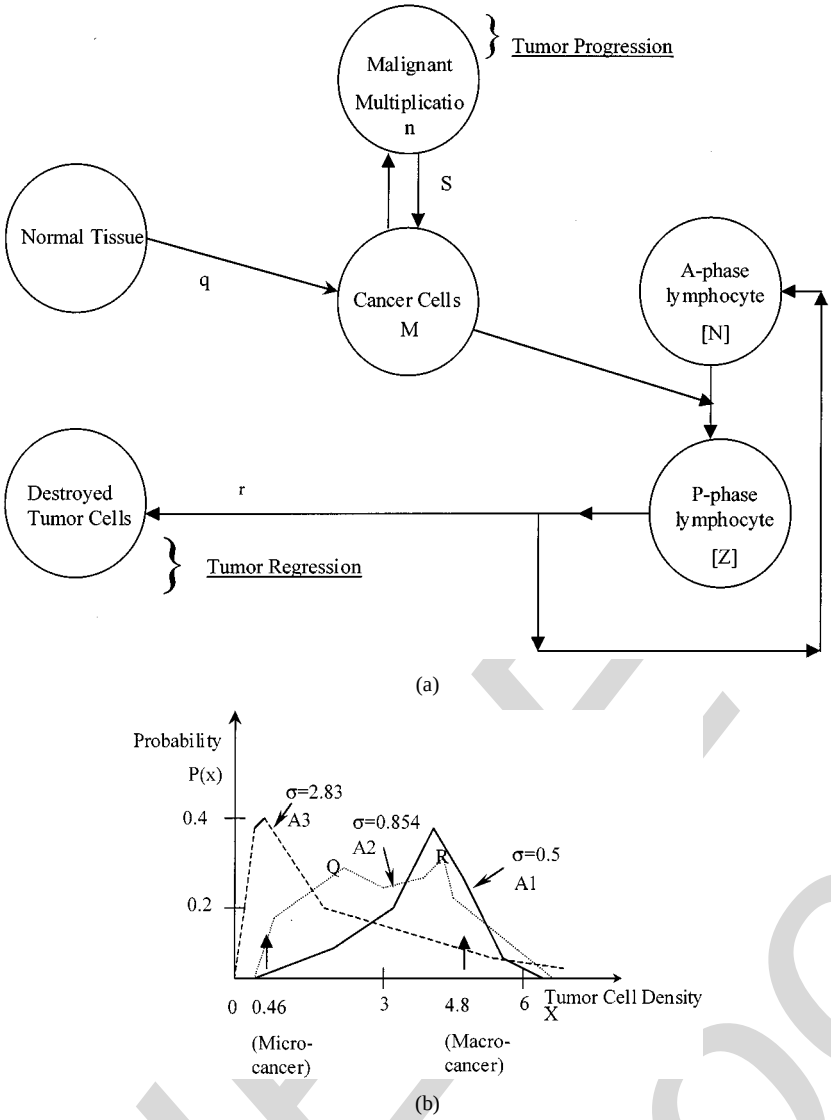

Fig. 5. (a) Immunocybernetic regulation of tumor, interacting with the lymhocyte cell existing in the active (A) phase and passive (P) phase, associated respectively with hunting aggressive mode and resting recuperating mode. Densities of various cellular constituents are shown in square brackets. The concept of duality of the two phases is in accordance with the notion of duality of two information states of the cell, alpha and beta, respectively. (b) Immunocomputational analysis of tumor destabilization induced by perturbations. Tumor regression and system instability actuated by increasing the perturbation of malignant cell destruction rate or of lymphocytic A-phase rate constant. Standard deviation of the perturbation increases from 0.5 to 0.85 to 2.83. Accordingly, the population curve shifts from A_1, A_2, to A_3. At the same time, the peak value of tumor cell density m decreases from 4.8 to 0.46, enabling tumor regression.

logical interactions [20], [47], we now attempt to explore the effect of fluctuation or perturbation on tumor immunodynamics, with a view to develop an algorithmic approach for investigating stability properties of systems in general. Of special interest is r, the tumor cell destruction rate, which varies inversely with the lymphocyte's active phase cycle time t' (as $r = (M + Z)/st'$). The more rapid is the predation (higher the predation rate constant k_1), i.e., less the active phase cycle time t', the higher is r. We now use the conventional approach of stochastic differential equations (SDEs) [23]. Let r_t denote the fluctuation of the r parameter around a mean value r

$$r_t = r + \sigma H_t \tag{13}$$

where σH_t is the perturbation with standard deviation σ. From (12), we obtain the SDE, where m_t denotes perturbation of m and W_t is the Wiener fluctuation amplitude

$$dm_t = [v + m(1 - um) - r(m/\{1 + m\})]\,dt + [\sigma m/\{1 + m\}]\,dW. \tag{14}$$

The corresponding Fokker–Planck equation of the probability density function $p(m)$ is derived as

$$\partial p(m)/\partial t = -\partial/\partial m[\{v + m(1 - um) - r(m/1 + m)\}p(m)] + [(\sigma^2/2)(\partial^2/\partial m^2)\{(m/1 + m)^2 p(m)\}]. \tag{15}$$

The steady-state solution for the last equation of probability density of (15) is

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

$$+\sigma^2 \ln(1+m)] \tag{16}$$

which enables us to see how the peak of probability density curve of tumor cell shifts as one increases the nonequilibrium perturbation intensity, i.e., the σ level. This shift implies a nonequilibrium phase transition.

C. Algorithm for Computing Tumor Instability

Perturb the k_1 parameter, the rate constant of A phase of lymphocyte. This will consequently fluctuate r, the tumor cell destruction rate, increase its standard deviation σ, and change the probability $p(m)$ of (16).

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Imunnodestabilization Algorithm
(i) Consider the range of increasing σ:
     e.g., 0 ≤ σ ≤ 3.
(ii) Use three representative values of σ:
    e.g., σ = 0.5, 0.85, 2.8.
(iii) Use some prototype values of the system
    parameters:
    u = 0.1; r = 5.95; v = 2.4; following [36].
(iv) Vary tumor cell density m:
    e.g., 0 ≤ m ≤ 6.
(v) Make the substitutions of σ, u, r, v, and m in (16)
    and perform computer simulation to calculate
    probability density p(m)
(vi) Construct three curves [Fig. 5(b)]
    for σ = 0.5, 0.85, 2.8, denoting increasing
    intensity of perturbing r
(vii) Fluctuate tumor cell reduction rate r by
    perturbing various parameters influencing r:
    e.g., perturbing the: T-cell cytotoxity, tumor
    temperature, radiation flux; cytotoxic flux;
    pO2-tumor oxygenation level.
(viii) Observe a change in the shape of probability
    density p(m)
    Indicating a possible phase transition
(ix) If no phase transition observed
    GO TO (i) step and change oscillation range
```

Steps (vii) and (viii) concern the generation and observation of phase transition are elaborated as follows. We know that variations in the above parameters are reflected as random variations of r, giving it a stochastic character [36]. In Fig. 5(b), we see that as σ increases from 0.5 to 0.854 to 2.83 (curves A_1 to A_2 to A_3), the probability density function exhibits nonequilibrium phase transition. The peak probability density of tumor cells shifts toward very low values of the tumor cell density m. For instance, tumor cell density shifts from 4.3 ("macrocancer focus"), to 0.46 ("microcancer focus"), i.e., a phase transition occurs

$$\text{increasing}\boldsymbol{\sigma}\text{ of immunodynamical perturbation}$$
$$\text{macrocancer focus}(m=4.3) \longrightarrow \text{microcancer focus}(m=0.4).$$

This corresponds to regression and elimination of the malignant tumor focus. By varying one or more immunomodulative parameters (as oxygenation, radiation, or temperature), we perturb the lymphocyte's A-mode information-processing rate constant. As a result, the tumor may have a predisposition to destabilize immunodynamically.

Now, consider the two immunocybernetic stages of tumor development mentioned earlier, namely: 1) the initial malignant "transformation" of the normal cell to the malignant cell and 2) the later process of tumor cell "replication," where the transformed malignant cell proliferates as a high output process, becoming clinically detectable. In such tumor growths ($\approx 10^9$ cells), the cancer cell replication (rate s) proceeds at a considerably greater intensity than the initial event of malignant transformation of the normal cell to the neoplastic cell (rate '$q' = 10^{-16}$ to 10^{-19}). Hence 'q' is negligible (≈ 0) and so is 'v,' since $v = qt''/st'$ as in (14). Thus, (16) reduces to

$$p(m) = \exp(2/\sigma^2)[(2-u-r)m - (1-2u)m^2/2 - um^2/3 + (1-r-\sigma^2)\ln m + \sigma^2 \ln(1+m)]. \tag{17}$$

Furthermore, the population of the initial malignantly transformed cells (m) is negligibly small compared to the 10^9 tumor cells formed by rapid replication. Thereby, (17) approximates to

$$p(m) = m^{\{[(2/\sigma^2)(1-r)]-2\}}. \tag{18}$$

D. Threshold Principle of Selecting the Perturbation Magnitude

We now explore the behavior of probability p according to three ranges of σ in the variation of r. In Fig. 6(a), we show the behavior of probability p, adapting our earlier analysis [16], [54] by plotting the probability of tumor cell density versus the increase of σ. In our study, we shift our attention to the variation of σ while r has specified value. Inspecting (18), it is clear that we have three regimes of behavior, demarcated by two separatrices, namely, at $\sigma = \sqrt{(1-r)}$ and $\sigma = \sqrt{2(1-r)}$.

- Case 1) $\sigma < \sqrt{(1-r)}$: The graph curve B_1 is unimodal with a definitive size of the active tumor focus.
- Case 2) $\sqrt{2(1-r)} > \sigma > \sqrt{(1-r)}$: The situation is denoted by curve B_2, with the most probable value being m_0, the steady point of the Ito SDE. The curve tapers toward higher values of m, where there is also appreciable probability, implying that the tumor focal population is still present.
- Case 3) $\sigma > \sqrt{2(1-r)}$: The line B_3 illustrates this regime, the graph being fully concentrated at zero value of tumor cell population and is reminiscent of a Dirac Δ function. The line B_3 indicates that the tumor density vanishes and the malignant focus becomes eliminated.

The value of r ranges between 0.01 and 1 as per experimental data [20]. For eliminating tumors, as a precaution, we should always exceed the higher limit of σ necessary to destabilize the growth. In Case 3, we observe that the malignant focus is eliminated. To satisfy condition of Case 3, we choose the lowest value of r, so the highest value of σ threshold could be considered. Perturbations having σ value above this threshold would assure of tumor instability. Thus, putting $r = 0.01$ in inequality

of Case 3, we obtain the conservative threshold condition for tumor destabilization

$$\sigma \,\text{of perturbation} > 1.41. \tag{19}$$

Hence, we may enunciate the threshold condition for eliminating clinically detected tumor.

Immunocomputational threshold principle for destabilizing a clinically detected tumor: A tumor may predispose to destabilize and regress if there is a sufficient fluctuation of lymphocytic informational rate constant or of the malignant cell reduction rate, so that the σ crosses the threshold of 1.41 or above. This variation may be achieved by correspondingly high variation of temperature, radiation, oxygenation, etc.

V. Experimental Confirmation of Algorithmic Approach to Instability

We present experiments that support our immunoinformatics model using perturbation of various parameters, so as to destabilize and regress tumors. We impart special emphasis to obstinate tumors.

Temperature Perturbation—Ewing's Bone Tumor: One of our specimen cases [52], [65] deals with a 17-year-old patient with end-stage Ewing sarcoma of left hip, rapidly going downhill with failure of radical surgery, 42 200 rad of cobalt-60 radiotherapy and T-12 chemotherapy (CVD protocol). He duly underwent a prolonged high-temperature fluctuation for 15 days induced by secondary fever, with fluctuation between 99 °F and 105 °F daily [see Fig. 6(b)]. The tumor and its extensive spread or metastasis showed a rapid permanent regression, confirmed by CT/Technitium-99 bone scans. The patient is well, ten years after the temperature perturbation event. Note that we calculate the σ of the temperature fluctuation to be 3.2, thus, satisfying the immunodynamical tumor instabilty principle of $\sigma > 1.41$. This illustrates the validity of our algorithmic approach of system instability and confirms the immunodynamical cancer treatment approach as ensured by the G–P Theorem of nonlinear dynamics.

Oxygenation Perturbation—Fibrosarcoma, Melanoma, and Prostate/Lung Carcinoma: The second set of experiments concerns perturbation of tumor oxygenation by repeated administration of endostatin (a collagen protein fragment) to young fibrosarcoma tumors, an aggressive tumor of soft tissue (see Fig. 7). Experiments were also successful on melanoma, Lewis lung carcinoma, and prostatic carcinoma. Endostatin markedly reduces the tumor oxygenation. Eight perturbartions of endostatin is given at intervals of several weeks causing fluctuation of blood supply and pO_2 oxygenation level [5], [16]. Thereby, the tumors, usually resistant to chemotherapy, undergo complete permanent dormancy and regression to a microfocus (see Fig. 8). We find that pO_2 of a young tumor is 11-mm Hg, which becomes 2.5-mm Hg during acute oxygen shortage in the tumor [60]. For Fig. 7, we note that the σ value calculates as 4.26, reinforcing the immunodynamical threshold theorem and system instability algorithm. The experiments well exemplify the immunocomputational phase transition of tumors.

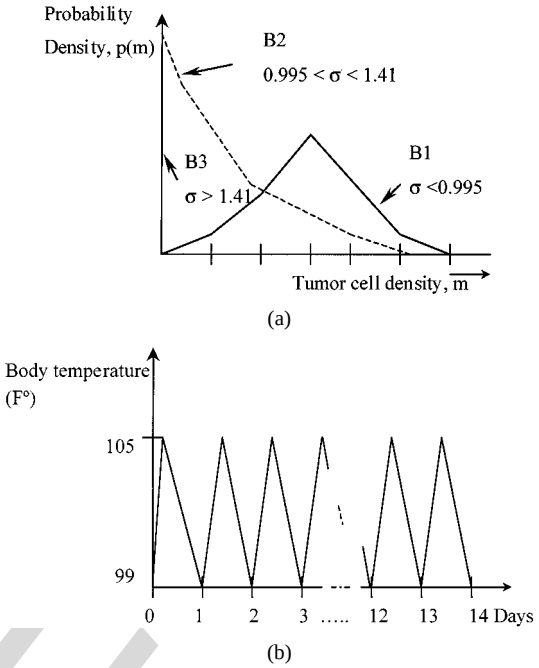

Fig. 6. (a) Immunodynamic threshold conditions of inducing instability and regression of clinically detected tumor. Parameter σ denotes standard deviation of the perturbation of malignant cell destruction rate or the lymphocytic A-phase rate constant. Increasing σ produces three types of behaviors: 1) curve A—definitive size of tumor and malignant activity; 2) curve B—smaller tumor activity; and 3) curve C—zero tumor density, i.e., tumor became unstable and it is eliminated. (b) Immunodynamic instability of Ewing tumor due to periodic temperature perturbations. Complete regression and disappearance of end-stage Ewing tumor of hip after the perturbation. Before the perturbative remission, the patient was deteriorating rapidly in spite of standard chemotherapy, radiotherapy, and surgery.

Chemical Perturbation—Neurogranuloma: One can regress trepanomic neurogranuloma mass in the brain using fluctuating temperature produced by introducing chemical or physical perturbations as by pharmacological, biochemical, or caloric measures, e.g., by nitrophenates or mucosaccharides or by radiofrequency diathermy through a selectotherm-scanning electronic equipment [52], [54]. The lymphocytes and giant cells are the immune cells here, the causative trepanoma cell is the pathological agent, and our immunodynamic instability model can be applied. Note that the parameter q and v vanishes in (11) and (12), as there is no malignant cellular transformation; we obtain a similar equation as (18). An effective procedure is administering the pharmacological or biochemical dose with tertian periodicity (every two days for three weeks) so that ten spikes of thermal perturbation from 98.4 °F to 104 °F is induced. Indeed, we calculate the σ value of this perturbation to be 2.87 and this fact satisfactorily confirms the instability principle and corroborates the utility of our approach. Actually, the efficiency of temperature perturbation in contrast to uniform high temperature had been earlier hinted by Jauregg's landmark clinical experiments [68], but this was an empirical conjecture without any theoretical explanation; our immunocomputational modeling appears to account for Jauregg's findings. Our modeling also helps one to optimize the therapeutic efficiency by increasing the perturbative σ. Maximized regression would be ensured if one uses higher σ by alternating the diathermia (high temperature) with

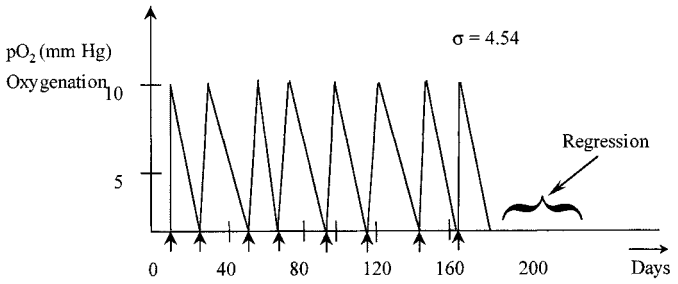

Fig. 7. Induction of tumor instability and regression of fibrosarcoma tumor by perturbation of oxygenation level using substance Endostatin.

hypothermia (low temperature, induced by neurochemicals as chlorpromazine with succinylcholine).

Radiotherapetic Perturbation or Hyperpulsed Hyperfractionation—Liver and Head-Neck Carcinoma: Our immunocomputational analysis predicts that more efficient tumor regression would be induced by increasing radiotherapetic perturbations. Hyper- and hypofractionation are two newer procedures in radiation oncology. One administers five exposures per week in normal fractions, ten exposures per week in hyperfractionation, and four exposures per week in hypofractionation. A typical dose in hyperfractionation is 1200 rad per exposure; 5000 rad per exposure in hypofractionation. It is found that, considering equal intensity of total radiation dose, there is increased tumor regression by hyperfractionation than with normofractionation [38], [52]. Further, if one decreases the number of weekly perturbations by using hypofractionation, one reduces efficiency of tumor regression. Hyperfractionation is effective in hepatic carcinoma and in head-neck cancer—two regions that are very resistant. Moreover, empirical evidence indicates that Dirac-like pulses of low duration and high-intensity energy (hence, high σ) can sterilize tumor metastasis efficiently with much less side effects [38]. Our perturbational analysis furnishes an explanation of this empirically observed phenomenon.

A. Limitations of the Approach—Cases Where Perturbations Can Not Induce Tumor Instability

Tissue Filters: Note that our model indicates that perturbation would not be able to induce immunodynamical instability of a tumor in cases where the perturbations are filtered or damped before reaching the target tumor. In such cases, the perturbations are considerably decreased by the time they reach the target tumor and become below the tumor destabilization threshold. Classic examples of such damping occurs when cytotoxic anticancer drugs are used that are metabolized in the liver, for instance, drugs such as pyrimidine analogues like 5-fluorouracil, cytosine arabinocide, asparaginase, and pentostatin. In such cases, the liver acts as a filter causing the damping. Hence, tumor instability may not be possible by high perturbation of flow rate of these drugs, these drugs should be excluded from our perturbative approach. Furthermore, other filters may interpose in the pathway of the perturbative agent before the agent reaches the tumor, such filters can be bone, fat, brain, pulmonary tissue, or gastrointestinal tissue.

Immunosuppresants or Surgery: Since our model is based on immunodynamical processes, there cannot be perturbation-induced tumor elimination if the immunological system is much compromised, e.g., if the patient is on high-dose immunosuppressive drugs as azathioprine, cyclosporine, antithymic globulin, etc. Further, our perturbative approach will not produce tumor regression if there is concurrent surgical intervention which alters the tumor cell–lymphocyte ratios and releases about 10^6–10^8 cancer cells in the bloodstream (not dealt with in our model).

VI. Algorithm to Detect Instability of a General System

Immunological algorithms have been used in pattern recognition, noise detection, data security, and image processing as also in biological problems of genetic sequencing [10]. We here probe how one can use the immunodynamic algorithmic approach to initiate an algorithm to detect instability in general systems under influence of perturbations or noise. Such a problem is an important one in science and technology. Two interacting systems are involved—target system and effector system—each system consuming or reacting with the other. The two systems correspond to the tumor and the immune system. Analogous systems could be predator–prey system in agriculture, reaction–diffusion system in chemical process plants, birth–death system in nuclear chain reactions, or parasite–host system in epidemiology. Researchers are generally interested in how instability can ensue in such dual systems under external perturbations or noise. To investigate this, we develop the following algorithm.

```
Imunnocomputing Algorithm to Detect Instability
(1) Initialize the population of target system
    (e.g., tumor system, Tu).
(2) Load the effector system population (e.g.,
    lymphocyte system, L).
(3) Construct the differential/difference equation,
    linking the population of the target Tu system,
    as acted on by the effector L system.
(4) Commence the fluctuation of a given parameter of
    the effector L system
(5) Actuate the Fokker–Planck equation.
(6) Obtain the steady-state solution of probability
    density function by summation/integration.
(7) Select prototype values of parameters of
steady-state equation (SSE).
(8) Present gradually increasing values of σ to SSE
    at a prefixed increment between successive
    values.
(9) Request immunodynamic response of SSE.
(10) Construct the probability density curves
    vis-à-vis the σ value.
(11) Select that threshold value of σ, for which the
    bimodal curve shifts to unimodality, producing
    phase transition and destabilization.
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VII. Concluding Remarks

Using the model of cybernetic control and systems engineering approach to the host–tumor system in immunology,

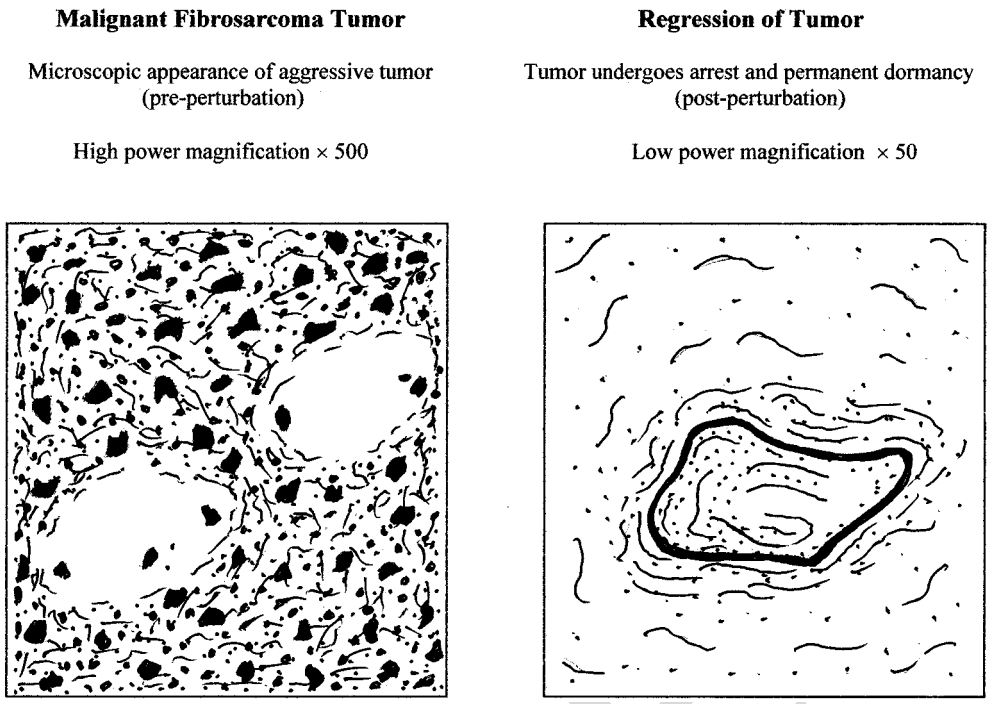

Fig. 8. Microscopic examination of experimentation of Fig. 7 signifying tumor destabilization by means of perturbation of oxygenation level (pO_2 intensity) using the angiostatin or endostatin chemical. (a) Void areas are fat cells. (b) Note the well-circumscribed microtumor focus, with a dense fibrous reaction (fibrotic tissue) around the tumor focus that is in a permanent dormant state.

we have attempted to establish an immunologically inspired algorithm to gauge the stability of a system. We have delineated how the recent developments of nonlinear dynamics and information processing in tumor functioning seem to open a novel approach to immunology and oncology. Using perturbation therapies based on immuncomputational analysis, one may induce instability in the tumor, actuating its elimination or regression. In particular, we have used the G–P stability theorem to give an informational, control, and cybernetic perspective on how systems in general can undergo unexpected gross instability and nonlinear phase transition due to small perturbations. Stability is an important problem in science, medicine, and engineering. For example, one may need to alter or design the stability of epidemiological/infective disease systems, electrical power grid systems, or agricultural prey–predator ecosystems, especially when these systems are subjected to unintended perturbations or disturbances.

Our immunoinformatics approach raises the question of the inherent susceptibility to gross destabilization and transition even in systems that are generally thought to be rock stable; this instability can be induced by small perturbation. The malignant tumor is viewed generally as an irreversible transformation which is maximally stable; the tumor is supposed to hardly ever lose its malignancy and becomes benign. In the present paper, however, we have seen that the addition of perturbative inputs can completely destabilize the tumor system, inducing elimination. This process is reminiscent of the well-documented natural phenomenon of spontaneous regression of cancer, predisposed by high-febrile temperature fluctuations. Since any system can be made unstable by judicious selection of the values of the pathophysiological parameters and perturbation amplitude, the algorithmic approach to immunodynamic instability may have great potentiality like natural tumor-regression process. This is permanent, without the risk of tumor recurrence, which generally happens with prevalent therapies.

The birth of the subject of immunocomputation and immunoinformatics, complementing neurocomputing, can be strategically exploited by computer scientists and engineers, besides biomedical scientists. Designing more comprehensive future algorithms for detecting and/or inducing instability in biological, oncological, computational, or technological systems can be a first step in that direction.

APPENDIX
IMMUNOINFORMATICS MODEL OF TUMOR INSTABILITY

We utilize the perturbational model of the stochastic approach to differential equation, the standard procedure of which is utilized from Horsthemke and Lefever [26]. SDEs are necessary to gauge the effect of perturbations and are readily obtained from the deterministic differential equation, by superimposing the Wiener fluctuation term (see below), these terms can be superimposed by adding to the deterministic equation. Now, let us construct the SDE of tumor cells when perturbations are given. Let us recapitulate (9)–(11)

$$Q = -(MN)/t' \tag{A-1}$$

$$dN/dt = -MN/t' + Z/t'' \tag{A-2}$$

$$dM/dt = q + [sM(1 - \{M/K\})] - r \cdot f(M). \tag{A-3}$$

The last term $rf(M)$ in (A-3) denotes intensity of tumor cells killed (Q), where r is rate of tumor cell destruction that correlates with the lymphocyte predation rate constant k_1 of the ac-

tive A phase or α-informational mode (see Section IV-B). Substituting the value of Q from (A-1) in $rf(M)$ term in (A-3)

$$dM/dt = q + [sM(1 - \{M/K\})] - MN/t'. \quad \text{(A-4)}$$

Eliminating N between (A-2) and (A-4)

$$dm/dt = v + m(1 - um) - r(m/[1 + m]) \quad \text{(A-5)}$$

or

$$dm = \{v + m(1 - um) - r(m/[1 + m])\}\, dt \quad \text{(A-6)}$$

where $v = qt''/st', r = (M + Z)/st', u = t'/Kt'', m = M{\cdot}t''/t'$, and $t = (s{-}q)t$, the latter implies that time is rescaled. The steady-state solution of (A-5) displays a remarkable cusp catastrophe, with critical points

$$v' = (1-u)^3/27u^2; \quad r' = (1+2u)^3/27u^2; \quad m' = (1-u)/3u. \quad \text{(A-7)}$$

Thus, we see that, as a function of the tumor cell destruction parameter r, the steady-state curves of m will present a bistability region and alteration of stability for $u < 1$. The bistable domain can be attained by decreasing the t''/t' or k_2/k_1 ratios. The ratio decrease can be achieved by increasing k_1, the active A-phase rate constant denoting the tumoritoxic capability of lymphocyte. Now, consider the condition where r fluctuates around a mean value r. As the time t ensues, we denote the fluctuating value as r_t, which is composed of two parts: r, which corresponds to the average state of the environment, and the fluctuating term σH_t, where H_t is the statistical perturbation with standard deviation σ. Thus, we get (13)

$$r_t = r + \sigma H_t. \quad \text{(A-8)}$$

This equation calls to mind the time-dependent Landau equation of critical phenomena. It is clear that for normal cytotoxic or immunological interactions, the fluctuations of the cancer cell destruction rate or A-phase rate constant vary much more rapidly than the macroscopic evolution of the tumor, the latter typically takes months or years. Then the correlation time of the fluctuation of r can be taken to be zero. Using statistical terminology of the central limit theorem, with E denoting the mathematical expectation value, we have $Er_t = r$ and, in terms of the two time scales t and t: $E(r_t - r)(r_t - r) = \sigma^2\delta(t - t)$. Now, consider adding the contribution of the stochastic component due to fluctuation of r in (A-5). We proceed as follows. Let us examine the term where r occurs in (A-5). This term is $r{\cdot}(m/\{1{+}m\}) = L$ (say). Consider the L's fluctuation (L_t) as r fluctuates in the form of r_t. This implies

$$L_t = r_t \cdot (m/\{1 + m\}). \quad \text{(A-9)}$$

Eliminating r_t between (A-8) and (A-9), we get $L_t = [r{+}\sigma H_t]{\cdot}(m/\{1{+}m\})$, i.e., $L_t = [r\{m/(1{+}m)\}]{+}[\sigma H_t\{m/(1{+}m)\}]$. Since, by definition, $L = r{\cdot}(m/\{1{+}m\})$ when r has the mean value r, we obtain

$$L_t = L + [\sigma H_t\{m/(1 + m)\}]. \quad \text{(A-10)}$$

Evidently. the term in square brackets in (A-10) is the stochastic term (say. S) contingent on fluctuation of r, i.e.,

$$S = \sigma H_t\{m/(1 + m)\}. \quad \text{(A-11)}$$

A. Derivation of the Probability Density Function

As per the Langevin formalism [26], we know that

$$H_t = dW_t/dt \quad \text{(A-12)}$$

where W_t is the Wiener amplitude or displacement of the fluctuation of the perturbing parameter r. Eliminating H_t between (A-11) and (A-12), one arrives at

$$S = \sigma\{m/[1 + m]\}dW_t/dt. \quad \text{(A-13)}$$

Hence, to obtain the effect of fluctuations of r, we should add this stochastic component S to the deterministic differential equation (A-5) and thereby obtain the SDE (15)

$$dm_t/dt = \{v + m(1 - um) - r(m/[1 + m])\} + (\sigma\{m/[1 + m]\}dW_t/dt). \quad \text{(A-14)}$$

Multiplying both sides by dt

$$dm_t = [v + m(1 - um) - r(m/\{1 + m\})]\, dt + [\sigma m/\{1 + m\}]\, dW_t \quad \text{(A-15)}$$

we can rewrite (A-15) as

$$dm_t = [F(m)dt] + [G(m)dW_t] \quad \text{(A-16)}$$

where the two terms in square brackets represent the contribution of the deterministic and perturbative process. Let us analyze (A-15) from the standpoint of the standard approach of Ito calculus (see [26]). We can treat (A-15) as the continuous limit of a discrete time model. Thus

$$[m_{t+\delta t} - m_t]/\delta t = [v + m_t - um_t^2 - rm_t/\{1 + m_t\}] + [m_t/\{1 + m_t\}]Q_t \quad \text{(A-17)}$$

where Q_t indicates the Gaussian random nature of variable r. Consider the steady-state solutions of (A-15) via the corresponding Fokker–Planck equation

$$\partial p(m)/\partial t = -\partial/\partial m[\{v + m(1 - um) - r(m/1 + m)\} \times p(m)] + [(\sigma^2/2)(\partial^2/\partial m^2)\{(m/1 + m)^2 p(m)\}]. \quad \text{(A-18)}$$

Denoting the probability density at steady-state solution by p, we obtain the steady-state solution for (A-18)

$$p(m) = \exp(2/\sigma^2)[-v/m + (v + 2 - u - r)m - (1 - 2u) \times m^2/2 - um^2/3 + (2v + 1 - r - \sigma^2)\ln m + \sigma^2 \ln(1 + m)]. \quad \text{(A-19)}$$

Equation (A-19) corresponds to (16). The rest of the paper after (17) can be readily followed as we subsequently use only elementary mathematics for deriving (17)–(19).

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