

NON-LINEAR DYNAMICS THEORY AND MALIGNANT MELANOMA

V.E. Orel^{1,2,*}, S.I. Korovin¹, J. Molnár³, V.B. Orel⁴

¹National Cancer Institute, Kyiv 03022, Ukraine

²Biomedical Engineering Department, NTUU “Igor Sikorsky KPI”, Kyiv 02000, Ukraine

³Institute of Medical Microbiology and Immunobiology, University of Szeged, Szeged H-6726, Hungary

⁴Medical Faculty, Bogomolets National Medical University, Kyiv 01601, Ukraine

Chaos theory (nonlinear dynamics) defines cancer as a complex adaptive system in which each cyclic point corresponds to the bifurcation at which changes in signaling pathways emerge. Quantitative assessment of chaos in digital medical images such as electron microscopy, histology and cytology sections collected from patients with malignant cutaneous melanoma employed the following calculation parameters: the irregularity of external contours, internal heterogeneity based on brightness distribution of macromolecules, chromosomes, organelles, inclusion bodies, cells and tissues, kurtosis, entropy and the asymmetry coefficient. The present study undertook a nonlinear analysis of the chaotic hierarchy of malignant melanoma. However, considerably more studies will need to be carried out to determine the exact interrelationship between different levels of the hierarchy in the biological system. Multidisciplinary collaborations are therefore essential to find evidence to answer questions that remain open to researchers and oncologists. **Key Words:** cancer, chaos (nonlinear dynamics), melanoma, hierarchical levels.

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The modern chaos theory (nonlinear dynamics) of living systems does not solely provide explanations for disorder in biology and medicine. This paper meets with a general acceptance that the terms chaos and nonlinear dynamics are used interchangeably. The chaotic nature of dynamical systems arises from the instability of their trajectories in a phase space under initial conditions [1–3].

The abundance of chaotic elements organizes in manners similar to the running functional systems. As a matter of fact, the study of self-organization patterns is a practical application of chaos theory to medical and biological systems [4]. Each harmonic could be independent in a linear system, whereas being related to other members of the series in a nonlinear one [5].

Chaos theory is a collective term referred to phenomena that describe systems as they change with time, e.g., attractors, bifurcations, fractals, catastrophes and self-organization. Nonlinear dynamics of seemingly random events can be predicted by simple deterministic equations. Given this mindset, unpredictable systems may appear to be stable on a larger scale and contain characteristics as clear boundaries and sensitive dependence on initial conditions. Small changes in the initial condition lead to a significant difference in the long run. Scientists have long sought to describe reality either by words or in terms of mathematics. While an excellent command of language enables one to express reality more flexible and yet more vague, equations provide a precise point with clear predictions [6–8].

Most human cancers exhibit spatial and temporal heterogeneity that impinges on the success of diagnosis, prognosis and treatment response. The complex dynamics of clonal evolution drives intratumor heterogeneity with variable patterns of genetic and

epigenetic diversity: gene and protein expression, signaling, structural architecture, oxygenation and other features of malignancy. Genome instability contributes to diversity between tumor cells and provides material for selection and evolution [9, 10]. The use of genomic instability in clinical practice is supported by findings from research on multiple types of cancer. After having examined a relationship between chromosomal chaos and metastasis, oncologists concluded that the treatment response depended on the extent of chromosomal instability [11, 12].

Over the past few decades, a great number of researchers has emphasized the role of nonlinear dynamics in understanding carcinogenesis with respect to fundamental ideas of Thompson on growth and form [13]. Likewise, Boveri introduced this concept in his somatic mutation theory [14], Warburg linked tumor growth and the bioenergetics of cancer cells [15], Turing described a critical role of mechanochemical signals [16], Szent-Györgyi examined the effect of free radicals in cancer development [17], Gurwitsch investigated the morphogenetic field [18] and Prigogine was among the first to draw our attention to order out of chaos [19].

Although differences of opinion still exist, Schrödinger suggested that self-organization was a defining property of living organisms, while inanimate nature tended to decrease order and thus give rise to entropy. He later proposed a concept of negentropy (negative entropy), where entropy was exported from a system. In other words, living organisms become more orderly through the use of negentropy. The term order refers to organization, structure and function, the very opposite of randomness or chaos [20].

Because oscillations are caused by external influences, they behave in a stochastic manner. This is the reason why chaos describes the basic aspects of the oscillation theory in biology and medicine. The role

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*Correspondence: E-mail: valeriiorel@gmail.com

Abbreviation used: ILK – integrin-linked kinase.

of negentropy in tumor growth and genetic resistance has been outlined in [21].

A broad perspective was adopted by Ukrainian researchers in their investigations devoted to the application of chaos theory to oncology [22–28].

The current review seeks to offer important insights into generalization and analysis of experimental and clinical data on causes, mechanisms of formation and manifestations of chaos in cancer development from the perspective of melanoma diagnosis. A full discussion of mathematical and computational approaches to nonlinear dynamics lies beyond the scope of this study.

CHAOTIC DYNAMICS IN CANCER

Cancer reflects a dynamical and multistage process. In a broad sense, cancer can be described mathematically by chaos theory. Changes in the cell shape and vasculature display increasing spatial chaos in heterogeneous tumor conglomerates [29, 30]. Earlier studies focused on the interaction between cancer and normal cells based on energy flows and entropy [31].

A reasonable question then arises: What is the interrelation between the mathematical chaos theory and biological processes associated with cancer? In a large body of biomedical literature, chaotic motion is understood to mean the motion wherein movement trajectories depend greatly on the initial condition. By assuming that accuracy of coordinate measurements is Δx and accuracy of speed measurements is Δv , we then can divide the phase plane (coordinate-speed plane) into parts with areas of $\Delta x \Delta v$ as shown in Fig. 1, *a*. Given the accuracy of initial conditions, the system is somewhere in the red shaded region of the phase plane. The uncertainty of a chaotic system increases with time by up to a size of $N(t)$ parts shaded red in Fig. 1, *b*. The rise in uncertainty is a fundamental characteristic of chaotic systems determined by:

$$N \approx N_0 e^{ht}$$

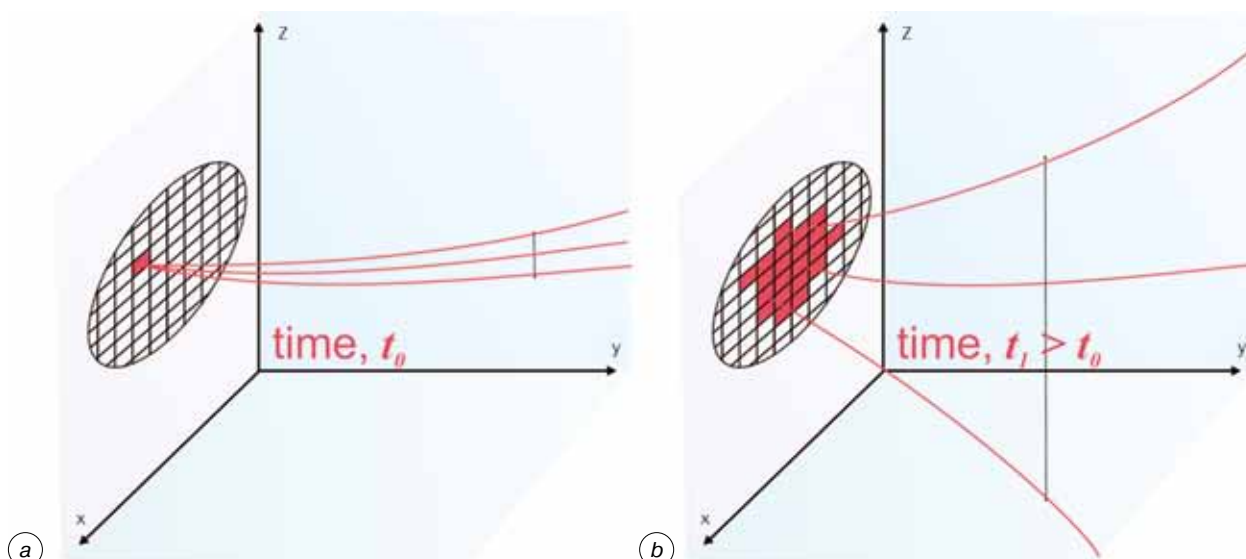


Fig. 1. Increase in uncertainty or loss of information in a dynamical system. The red shaded squares illustrate: *a* — the uncertainty of the initial condition at the moment t_0 ; *b* — the accessible state at the moment t_1

The Planck constant, h , is associated with information entropy and the Lyapunov exponent (i.e., the rate of divergence of nearby trajectories).

The human host is a hierarchically ordered nonlinear biological system. The complex nature of higher levels as compared to lower levels is a key property of the structural hierarchy. Structural elements contained at a lower level can exhibit transition into chaotic behavior on a larger scale. For instance, C, H, N, O, P, S atoms could play a role of chaotic elements compared to biological macromolecules. In the same way, nucleic acids and protein macromolecules relative to chromosomes, cells relative to organs, etc. could refer to the elements of chaos. In addition, the reverse influence of chaos at higher levels upon lower structural levels should also be considered [32]. Self-organization patterns obey the laws of chaos and can affect oncogenesis. A series of random factors have a significant impact on self-disorganization across all levels of the hierarchy in the human body during its development. Self-disorganization can cause the proteins encoded by proto-oncogenes and tumor suppressors to malfunction. Many of these proteins regulate cell cycle signaling, apoptosis pathways, genetic stability, differentiation and morphogenesis [33].

Fig. 2 provides a schematic overview of chaos model for oncogenesis [30–36]. According to Feigenbaum, each cyclic point corresponds to the bifurcation point at which changes in signaling pathways emerge at different levels of the hierarchy in the human body [34, 35]. Multiple shifts in the signaling act as a switch from nonlinear dynamics of cell cycles normally observed in living organisms to pathologic proliferation [37].

At the molecular and submolecular levels, much of research attention must be given to quantum chaos. Prigogine and Stengers have determined quantum chaos by the irreducible probability of a quantum system to distribute energy. Many pathophysiological processes alter the motion of atoms. For instance, inflammation is accompanied by a rise in body temperature, and

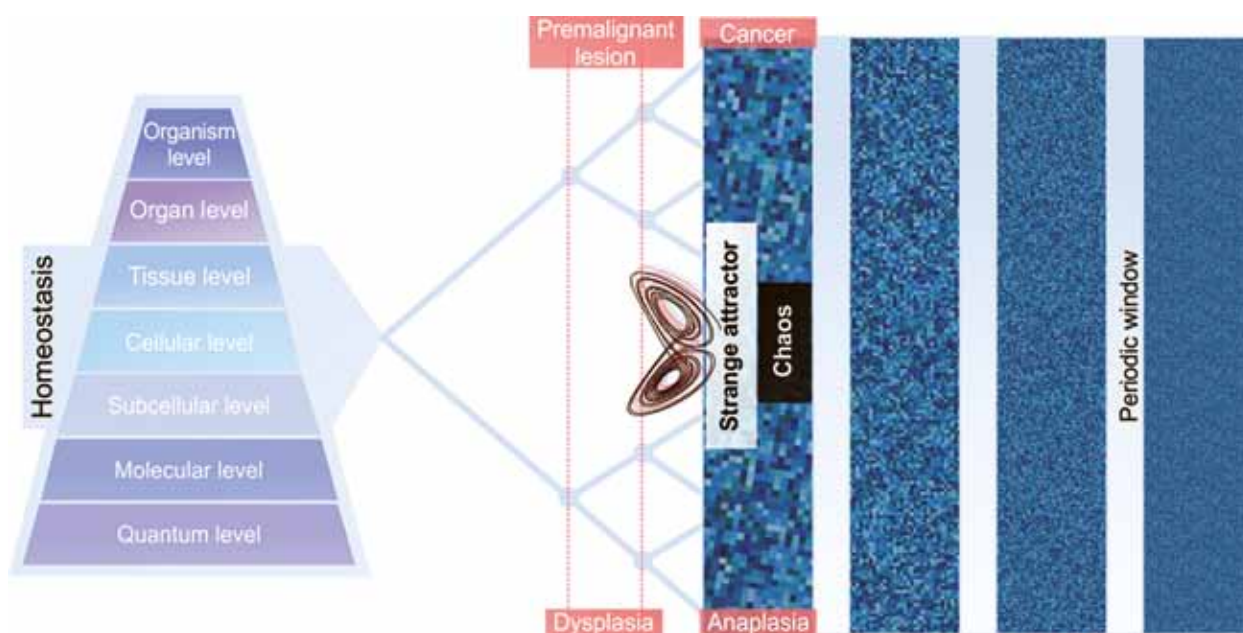


Fig. 2. Chaos model for oncogenesis. Perturbations occurring at different structural levels of the hierarchy in the human body induce bifurcations and produce a shift in morphological and genetic characteristics of a tumor. The chaotic bands (the areas filled with texture) of bifurcations lie between narrow windows in which chaos reverts to periodic motion

under such conditions, the Brownian motion greatly contributes to the chaotic motion of atoms. As each atom has its own energy threshold, one question that needs to be asked, however, is what energy has to be applied to cause quantum chaos. Excitation and fluctuations may initiate chaotic motion leading to charge transfer across a molecule at a certain energy level [19].

Cancer, as a rule, is associated with chaos of free radical-induced oxidative stress. For this reason, free radicals are among the factors to modulate the chaotic dynamics of carcinogenesis at the quantum level [38].

Tumorigenesis and metastasizing initiate chaotic dynamics of mechanochemical interactions between tumor and normal cells [39]. It has now become clear that mechanical stress has a wide range of effects in biomedicine. Not only do mechanical forces deform cells and molecular structures, but also mechanical energy can be converted to chemical and vice versa. This phenomenon is commonly known as the mechanochemical effect. Edelman in his topological theory postulated that mechanochemical interactions regulated cell adhesion and were involved in immune reactions [40]. Besides, the immune system is thought to behave in a nonlinear manner in response to malignant cell growth [41].

Complex quantitative modelling has revealed that the rate of entropy production is higher in cancer cells than in normal ones, even when an external force field is not applied [42]. Self-disorganization originates from antagonism of stimulating and silencing signals in cause and effect relationships at the margins of adjacent hierarchical levels. Such effects are also to consider in the dynamics of reacting physicochemical systems during oncogenesis. In fact, a combination of local and systemic treatments for cancer is subject to certain limitations on additive and synergistic interactions. A major source

of uncertainty lies in the interpretation of values for the parameters employed in the chaotic bands of the hierarchy in biological systems.

PARAMETER ESTIMATION FOR CHAOTIC DYNAMICS OF CANCER

In order to analyze nonlinear dynamics of digital medical images, for example, electron microscopy, histology or cytology sections collected from malignant tumors, the following calculation parameters were used: the irregularity of external contours and internal heterogeneity based on brightness distribution of macromolecules, chromosomes, organelles, inclusion bodies, cells and tissues. In addition, quantitative assessment employed statistical parameters such as kurtosis, entropy, asymmetry coefficient [43, 44].

Fractals are spatial figures that exhibit self-similarity or simply shapes with the fractal dimension. They are capable of describing chaotic behavior at some hierarchical levels. Having the property of self-similarity means that fractals do not change their spatial characteristics across different scales: both up and down the hierarchy. The fractal dimension is one of the geometric properties to measure the complexity of the shape, while a noninteger value is typical of chaotic attractors [45–47].

Nonlinear dynamics and fractals are naturally paired since chaotic behavior carries over repeated patterns to previous starting trajectories (the Lorenz model). The connection between chaos theory and fractal geometry provides support for the effective application of these concepts to biomedicine, namely cancer theranostics [48]. Many biological systems can display their possible states as attractors, comprising the points around which trajectories accumulate. Perhaps, the adoption of an attractor model in cancer biology would help to deepen our understanding of tumor heterogeneity and its dynamics, hence improve personalized

cancer diagnosis and treatment [49]. While a variety of attractors exists in the present time, Kauffman was first to propose the idea of “the cancer attractor” which had evolved from his study on complex dynamics. There now is ample experimental evidence that perturbations in dynamic signaling pathways can drive cell fate and result in cancer development. As cells reach the attractor states through changes to their genotype and phenotype, it becomes possible to link each state with a gene expression profile and identify each cell type among the entire tumor. Gene regulatory networks provide the ability to generate diverse and distinct cell phenotypes around a single genome in malignant cells. In the same way, modeling of gene regulatory networks might be explained by the cancer attractor [50].

Lyapunov exponents characterize the behavior of nearby trajectories in the phase space. They give a rough measure of chaos and examine whether a system depends on initial conditions. A set of the Lyapunov exponents (i.e., the Lyapunov spectrum in which the number of state variables defines the number of exponents) is related to the fractal dimension of the strange attractor. The Lyapunov spectrum determines regions of stable behavior within the attractor. A positive exponent reflects the average rate of exponential divergence (expanding axis), whereas a negative exponent reflects the average rate of exponential convergence (contracting axis). As far as a zero exponent is concerned, one is dealing with a stable periodic attractor [51].

The concept of time evolution uncovered signatures of chaos in research studies. The first oscillations became apparent from observations of the signal amplitude dependence on time when motion signals did not exhibit periodicity. The above test was not fully reliable since the period of motion could be too long to determine and some nonlinear systems could display quasiperiodicity with two or more periodic signals of incomparable frequency. Although the resulting signal in the second case may have seemed to be nonperiodic, after signal splitting some oscillation patterns were recognized as periodic. The analysis of oscillation behavior often employs the phase plane approach.

The first experimental construction of a chaotic attractor in the phase plane was carried out by Lorentz, who was trying to predict long-term meteorological patterns. He later associated minor changes in the initial conditions (e.g. fluid viscosity, thermal conductivity, temperature) with a significant shift in atmospheric convection. Thus, the Lorenz attractor was built to characterize a dissipative system exhibiting stochastic dynamics. Because of the extreme sensitivity to initial conditions and shape of the attractor, Lorenz findings had been collectively called the “butterfly effect”. Nowadays, the question whether the flap of a butterfly’s wings in Brazil can cause a tornado in Texas has been addressed by researchers across many fields [52].

Lorenz has demonstrated that the Earth atmosphere behaves in the manner described by strange attractors. Continuous chaotic flows and periodic windows exist due to internal interactions in nonlinear dynamics of atmospheric circulations. Further investigations found that

biological systems were under the same laws of nonlinear dynamics. However, it should be noted that chaos, in this case, arose as a consequence of interactions within the dynamical system rather than a response to an external influence. The exponential growth of disturbances in initial conditions makes it nearly impossible to predict the long-term behavior of a given dynamical system.

In order to describe the long-term behavior more accurately, the current study designed a special algorithm to calculate the spread parameter of trajectories in the phase plane based on the pseudo-phase plane approach [53]. The spread parameter was used to analyze nonlinear kinetics of blood mechanoemission in the course of Lewis lung carcinoma growth in tumor-bearing animals, contour-based tracking of tumor cells, histological structures and optical density of MR images obtained from patients with gastric cancer [54].

In recent years, much progress has been made in the development of parameter estimation techniques for nonlinear dynamical systems. With advances in diagnostic modalities, the use of parameter estimation for chaos in medical images has experienced major improvements. Nonlinear dynamics can provide additional objective criteria for a more definitive diagnosis of cancer in a specific organ. However, the integration of parameter estimation and its values for the whole host remains challenging.

CHAOTIC HIERARCHY OF MALIGNANT MELANOMA

Melanoma is a potentially lethal malignant tumor that arises from melanocytes. The tumor tends to metastasize beyond the primary site and becomes resistant to chemotherapy. Delayed diagnosis of malignant melanoma correlates with a poorer prognosis. Therefore, early detection and accurate staging increase the chances for successful treatment [55]. In the past decades, the incidence of melanoma has steadily increased contributing to common cancer types in Caucasians. More than half of patients are diagnosed with melanoma ≥ 1.0 mm in Breslow thickness. Early detection of melanoma is a strategic priority at present [56]. In order to quantify heterogeneity observed in medical images and biomedical signals at different levels of the hierarchy, we adopted methods of nonlinear data analysis. The chaos and clues algorithm is a practical way of dermatoscopic screening that examines asymmetry in color or structure. In contrast to existing algorithms, the chaos method can be used for any pigmented skin lesion regardless of origin. Previous studies have associated chaos with such diagnostic imaging criteria as architectural disorder, contour asymmetry and pattern asymmetry of a lesion [57]. The simplest employment of the algorithm quantified symmetry over chaos to determine whether a lesion was benign or malignant [58]. Examining the overall architecture of an entire lesion by the chaos method was reported to be highly discriminative and had high levels of interobserver agreement. Hence, there has been a growing need for a quantitative parameter in medical imaging, Doppler ultrasonography and signal analysis.

Regardless of patient gender and age, digital dermoscopy, microscopy and ultrasound images from the National Cancer Institute archives were assigned to 2 groups: patients with pigmented nevi and patients with primary malignant melanoma < 1.3 mm thick [59].

Fig. 3 demonstrates dermoscopy images of malignant melanoma in the surface layers of skin and distribution function of their brightness levels. In addition, Table 1 provides the results obtained from the quantification analysis of spatial chaos. The energy of brightness levels and contour irregularities quantified image heterogeneity. Further analysis revealed

that values of the contour irregularity as well as the energy of the brightness level were 31% and 99% greater than those of images with pigmented nevi, respectively. Digital dermoscopy images of malignant melanoma were found to be more heterogeneous than the images with pigmented moles.

Table 1. Evaluation of spatial chaos in digital images of the tumor surface

Tumor type	Irregularity, contour irregularity parameter, r.u.	Image heterogeneity, energy of brightness levels, r.u.
Nevus	1.3 ± 0.1	1.1 ± 0.4
Malignant cutaneous melanoma	$1.70 \pm 0.08^*$	$2.2 \pm 0.2^*$

Note: *Significant difference ($p < 0.05$).

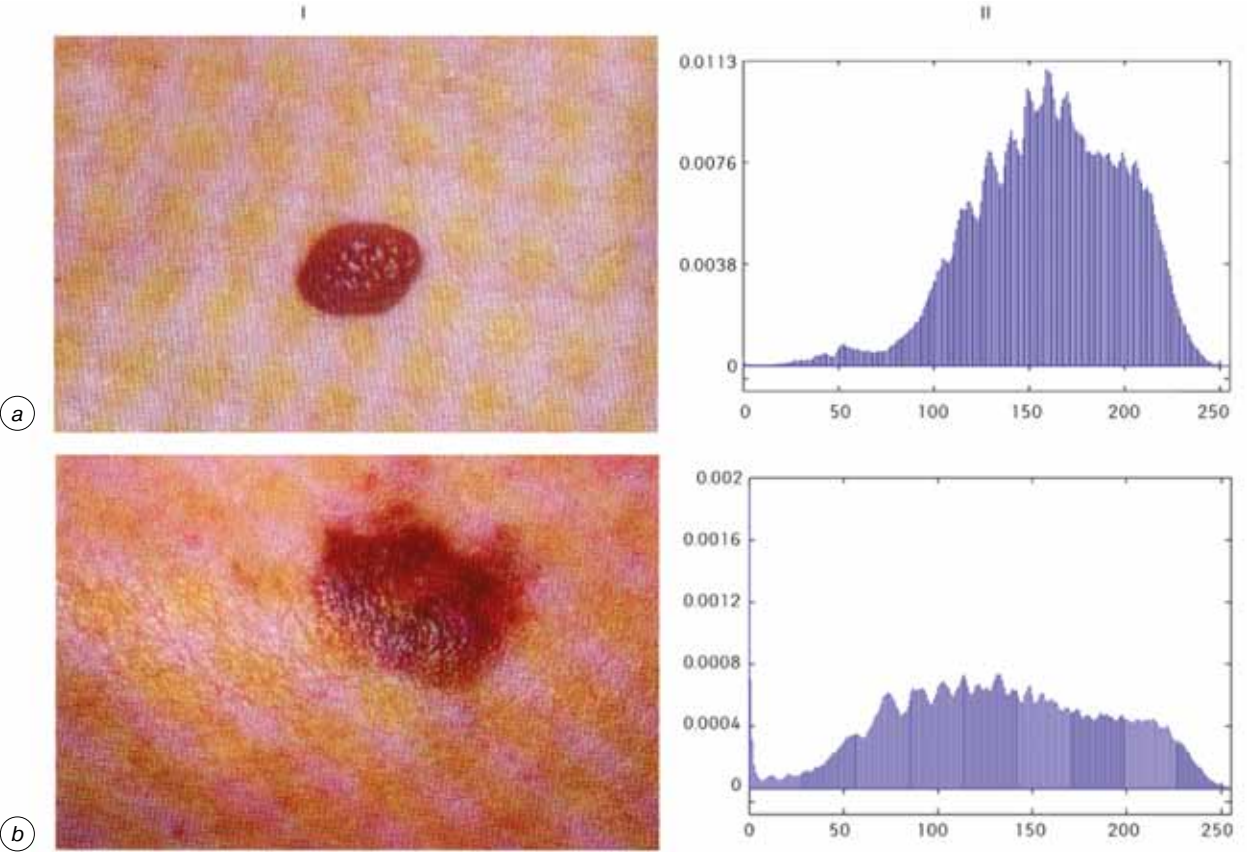


Fig. 3. Dermoscopy images of the tumor surface and the distribution function of brightness levels: *a* — pigmented nevi, *b* — malignant cutaneous melanoma. I — dermoscopy images of skin neoplasia, II — the distribution function of brightness levels, where the x-axis is equal to the brightness level (r. u.); the y-axis is equal to the distribution function of the brightness levels

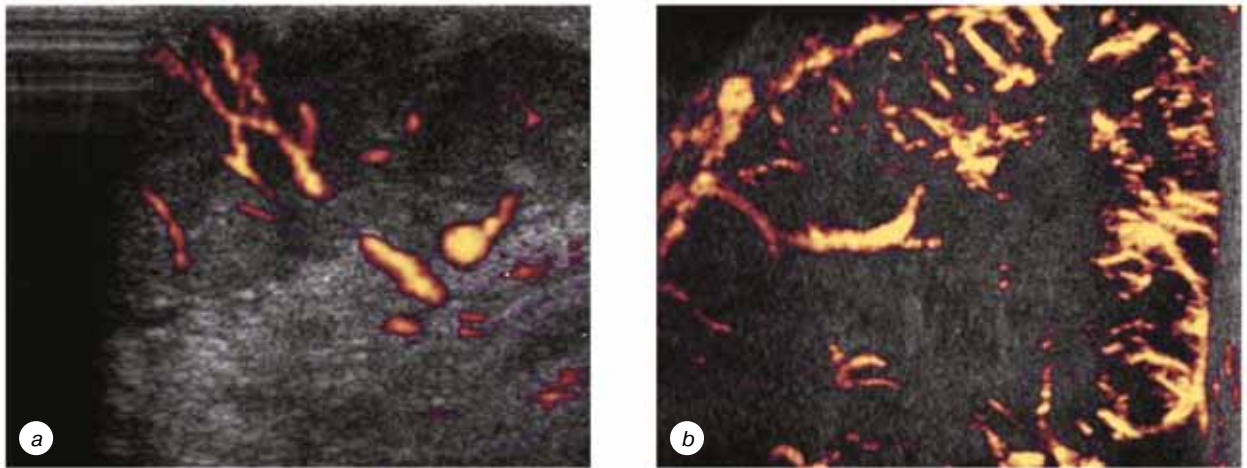


Fig. 4. Doppler ultrasound imaging of cutaneous melanoma blood vessels: *a* — nevi; *b* — melanoma

Table 2. Heterogeneity of tumor vasculature observed in digital Doppler imaging of different types of pigment neoplasms of skin

Tumor type	Fractal dimensions, $d \pm SD$
Nevus	1.50 ± 0.05
Malignant cutaneous melanoma	$1.7 \pm 0.1^*$

Note: *Significant difference ($p < 0.05$).

Having discussed the implications of nonlinear dynamics in dermoscopy, this part moves on to investigate sonographic heterogeneity of tumor vasculature in Doppler images (Fig. 4). The fractal analysis of images (Table 2) obtained from patients with pigmented

nevi and primary melanoma showed that the malignant tumor vasculature was highly heterogeneous and more chaotic compared to a nevus.

Fig. 5 compares microscopy images of normal skin cells with melanoma cells and the distribution function of their brightness levels.

Table 3 presents the summary results for heterogeneity quantifications using the fractal dimension and entropy of brightness levels in normal and tumor cells. These findings concluded that malignant melanoma

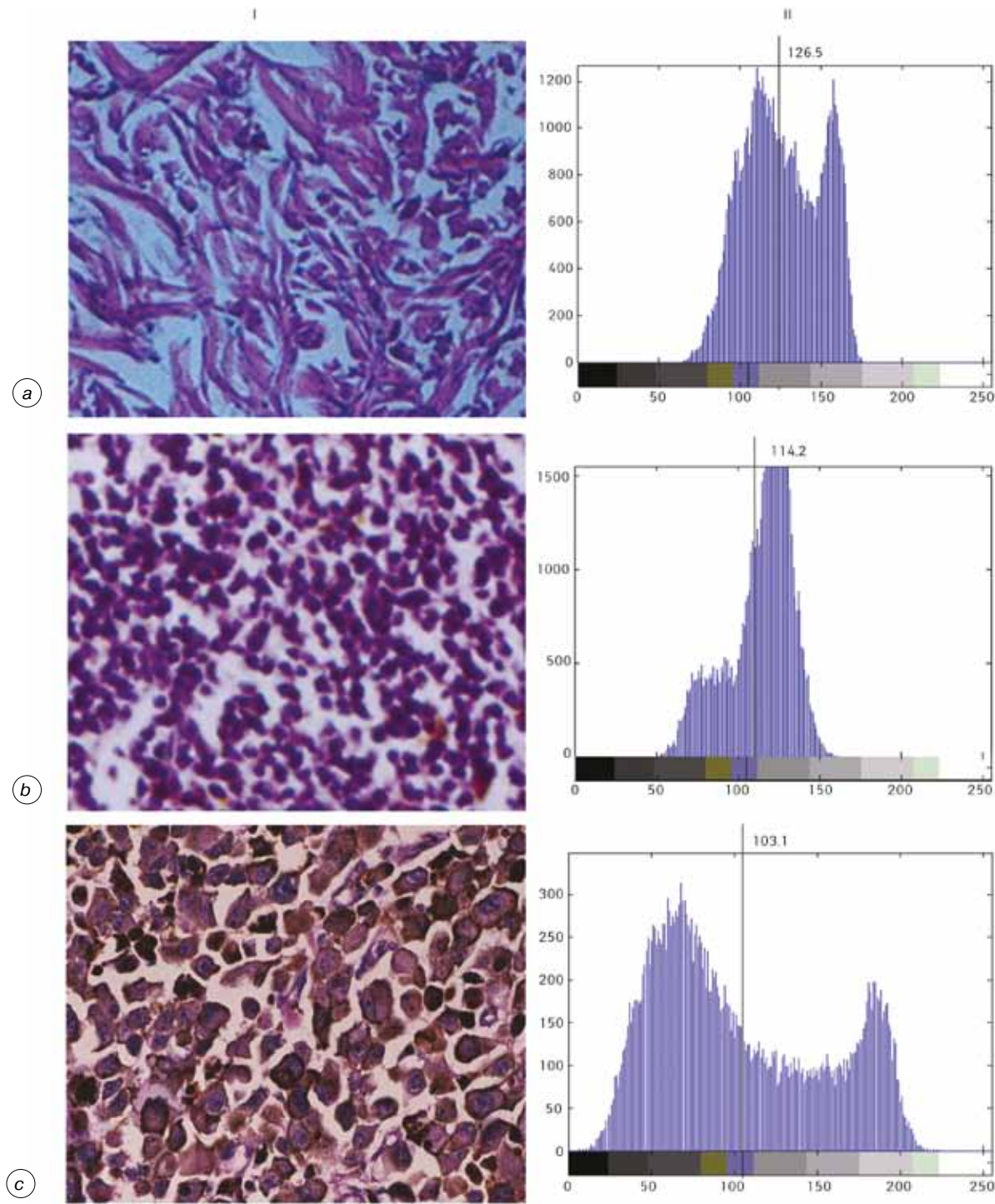


Fig. 5. Comparison of microscopy images of samples of normal skin and melanoma samples and the distribution function of brightness levels: *a* — normal skin; *b* — nevus; *c* — malignant melanoma of a giant cell-rich type. I — microscopy images of the skin; hematoxylin & eosin; $\times 200$, II — the distribution function of brightness levels, where the x-axis is equal to the brightness level (r.u.); the y-axis is equal to the distribution function of the brightness levels

Table 3. Heterogeneity observed in digital images of normal and tumor skin cells

Cell type	Parameters	
	Fractal dimensions, $d \pm SD$	Entropy of brightness levels, r.u.
Normal skin cells	1.803 ± 0.053	4.496
Nevus	1.459 ± 0.035	4.253
Malignant melanoma of a giant cell-rich type	1.858 ± 0.003	5.144

cells had a greater tendency to exhibit spatial chaos at the cellular level than nevi or normal skin cells.

As is well-known, integrin-linked kinase (ILK) is an enzyme involved in cellular signaling to promote tumor cell migration, invasion and growth in cancer patients. Elevated expression of ILK often correlates with melanoma stage and grade. For this reason, chaos measures at the molecular level were based on ILK expression in primary malignant melanoma cells. As can be seen from Fig. 6, different levels of ILK expression were reported in the tumor tissue samples [60]. The five-year survival rate for melanoma patients with low expression of ILK (0; 1+; 2+) was by 14% higher than for the patients with overexpressed ILK levels (3+).

The estimated fractal dimensions for different ILK levels in melanoma are provided in Table 4. There was a significant correlation between an increase in the fractal dimension and ILK expression by tumor cells.

Apart from dermoscopy, Doppler and microscopic image analysis, the present study sought to examine

Table 4. Fractal dimensions of different ILK expression in malignant melanoma

Image	Level of ILK expression	Fractal dimensions, $d \pm SD$
a	tumor does not express ILK (0)	1.588 ± 0.040
b	low ILK expression (1+)	1.671 ± 0.051
c	moderate ILK expression (2+)	1.734 ± 0.055
d	high ILK expression (3+)	1.843 ± 0.034

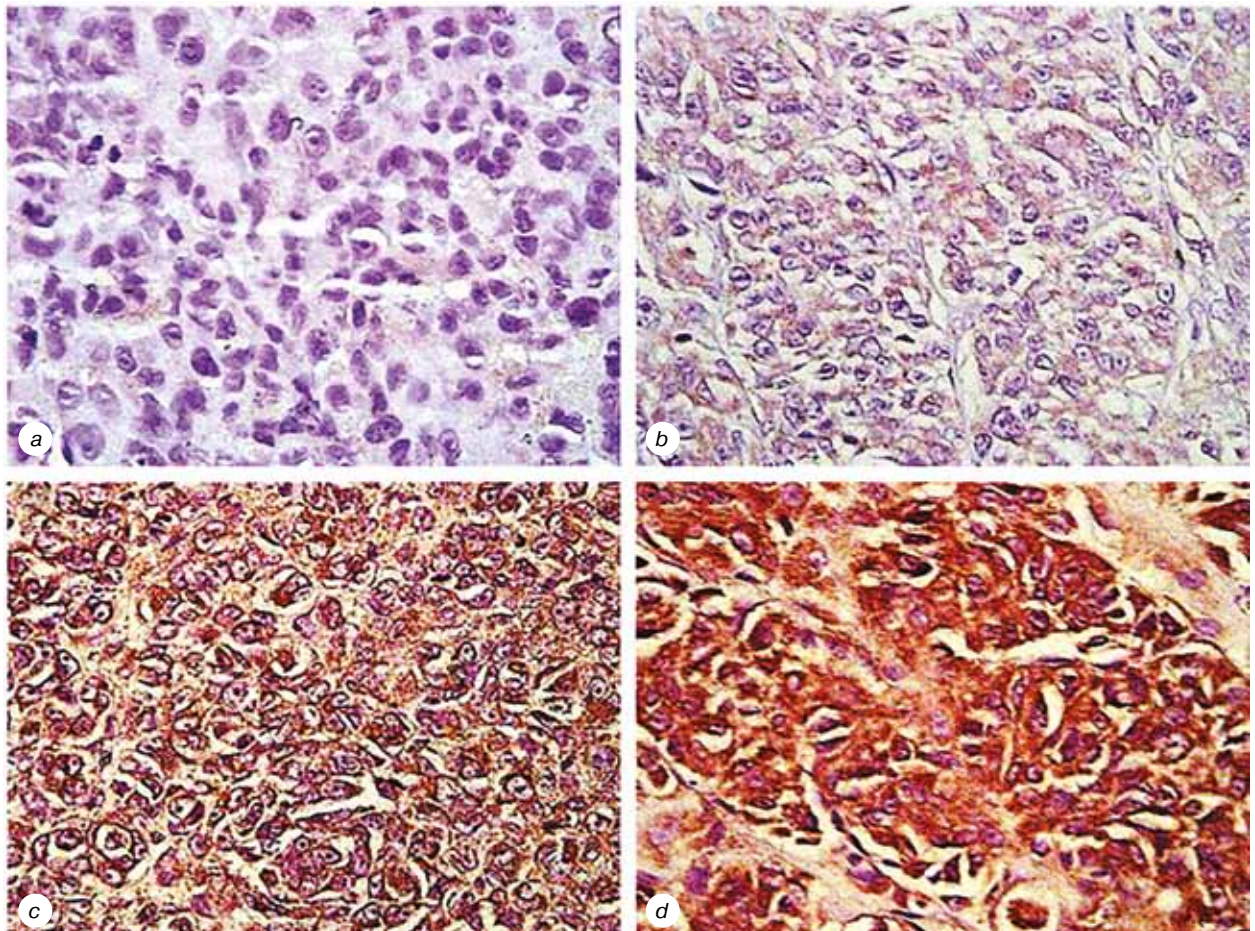
changes of blood chemiluminescence. Periodograms in Fig. 7 estimate the density of the spontaneous chemiluminescence signal recorded from blood serum in patients with malignant cutaneous melanoma and healthy individuals. The rates of divergence in the periodograms are highlighted in Table 5. It can be seen from the data that the divergence was 21% higher in patients with melanoma. Our findings reflected an increasing tendency towards stochastic (chaotic) processes at the quantum level in the blood of patients with melanoma.

Table 5. The rate of divergence in periodograms of the spontaneous chemiluminescence signal recorded from blood serum

Group	Spread parameter, S, r.u., $M \pm m$
Healthy individuals	153.9 ± 7.0
Patients with malignant cutaneous melanoma	$186.2 \pm 6.0^*$

Note: *Significant difference ($p < 0.05$).

Taken together, these results provide additional evidence that one of the fundamental features of non-linear processes in malignant melanoma was a decrease of deterministic chaos and, on the other hand,

**Fig. 6.** Expression of ILK in malignant melanoma: a — negative ILK expression when melanoma cells do not express ILK (0); b — low ILK expression (1+); c — moderate ILK expression (2+); d — high ILK expression (3+). Immunohistochemical staining; $\times 400$

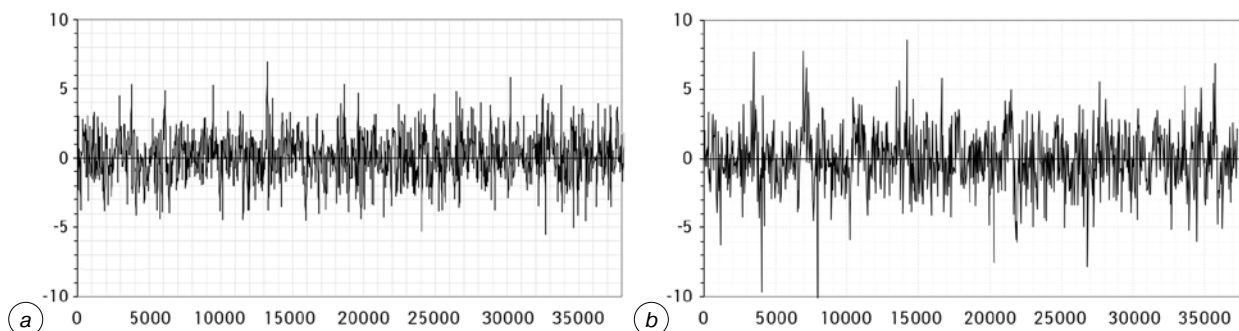


Fig. 7. A typical periodogram of the spontaneous chemiluminescence signal recorded from blood serum: *a* — people without disease; *b* — patients with malignant cutaneous melanoma; the x-axis represents the frequency, Hz; the y-axis represents the ratio of signal density to noise, r.u. (logarithmic scale)

a significant rise of stochastic phenomena across all levels of the hierarchy in the human body. However, considerably more studies will need to be carried out to determine the exact interrelationship between different levels of the hierarchy.

CONCLUSION AND FUTURE RESEARCH

Despite this interest, few researchers have focused on the application of chaotic dynamics to cancer theranostics. As a natural progression of the present work, future investigations should try to elucidate the links between physics, mathematics and life sciences. Multidisciplinary collaborations are therefore essential to find evidence to answer questions that remain open. Further advances in computing technology will provide a promising platform for cancer diagnosis and treatment based on the quantum, molecular, cellular and organ levels which may serve to solve the periodic windows of chaos and hence use nonlinear dynamics in clinical practice.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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