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Mesoscopic Cell Mechanobiology and the Problem of Cancer

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Abstract

Statistically based model of the DNA ensemble evolution allowed the formulation of mechanobiological approach linking the open complex dynamics and different scenario of gene expression related to normal and cancer cell behavior. It was shown the correspondence of open complex dynamics to specific type of criticality in mesodefects (open complex) ensemble (the structural-scaling transition) in the presence of qualitative different nonlinearity of the mesoscopic potential associated with the epigenetic landscape. The role of open complexes is similar to the mesoscopic defects and provides the cell plasticity or the cell fragility depending on the structural susceptibility of the cytoskeleton structure and the types of collective modes of defects (open complexes). These modes are responsible for the DNA transformation leading to the natural cycle of gene expression and spontaneous cell division as the cancer precursor. The WTMM analysis of the phase thickness fluctuations after the Laser Interference Microscopy of living cells shows the log-normal and power law statistics for normal and cancer scenario that are linked to multi- and monofractal dynamics of open complexes.

Keywords: mechanobiology; DNA transformation; open complexity; Laser Interference Microscopy

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Introduction

Cells reveal the structural organization to promptly adapt their mechanobiological environment in realization of fundamental vital cellular functions [1,2]. The mechanobiology properties of living cells are mediated by the cytoskeleton (CSK) representing a dynamic network of filamentous proteins composed of actin filaments, microtubules, and intermediate filaments [3,4]. Components of the CSK play a key role in motility, transport and cell division, providing essential scaffolding on which metabolic processes occur. Therefore, cytoskeletal morphology is thought to be a valuable indicator of cell injury and functionality [5]. Inner cytoskeleton structure also provides 'privileged' pathways along which enzymes and substrates are coherently organized and oriented, in order to optimize their interactions [6,7]. The variety of the mechanisms of structural relaxation could be associated with fundamental property of the cells qualified as the cell plasticity and the cell damage [8].

Plastic deformation as the unique mechanism of the defects induced momentum transfer and the structural memory provides specific CSK organization in mechanobiological environment. The cell plasticity can be considered as the leading mechanism providing the vital CSK properties, including the cell self-organization up to the cell division. The cell division being the vitality ground has also natural links to the defects behavior that provides the evolutionary controlled cell division (due to the preceded plasticity) or the fragility due to the pathological CSK changes leading to the spontaneous cell division. The duality of defects in the realization of the vital cellular functions (plasticity, damage, damage-

failure transitions) is stimulating for the consideration of the CSK structure as out-of-equilibrium system with defects taking into account the fundamentals of defects in the matter properties as the localization of the symmetry groups [9]. Multiscale mesoscopic approach in the simulations of biological systems with defects (biological molecules, cell and tissue) are analyzed in the mechanobiology statement to link the qualitative changes of behavior of mesoscopic systems as the specific type of criticality (structural-scaling transitions) [10]. The mesoscopic approach is considered as the "middle-out" paradigm for the description of coherent dynamic behaviors in biological systems and depends upon the choice of leading mechanisms and corresponding mesoscopic thermodynamic (and kinetic) parameters [11,12]. The mechanobiology in the combination with molecular genetic approach could provide the actual direction for objectification of pathological tendencies in the living cells in the case of cancer. The methodologies, numerical and experimental techniques coming from mechanobiological approach and combined with multi-scale signal processing are the ground of the advanced concepts of biological systems evolution related to the role of collective phenomena [13]. "In-situ" study of the cell mechanobiology by the laser interference microscopy (LIM) with the following definition of "meaningful" collective degrees of freedom allows the determination of dynamic stability of biological systems, including tissue, and they qualitative changes with "damage" accumulation with an application to cancer progression.

Open complex dynamics: DNA and cell transformation

The open states or the bubbles appear as the areas of local denaturation due to the breaking of the H-bonds, that leads to the local opening of the base pairs, Figure 1. The open complexes develop due to the activation of specific subsets of gene expression patterns revealing the intrinsic stochasticity in gene expression, wide range of gene patterns providing different possible phenotypes [11]. The open states provides the DNA transformation as the mechanisms of the cell plasticity and the cell division.

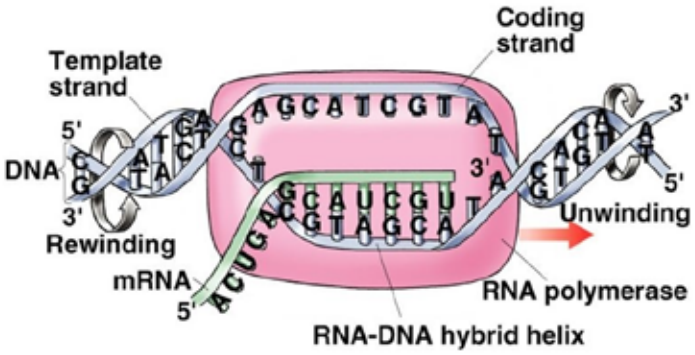


Figure 1: DNA structure and open complex formation.

Conformational transitions, the formation of opening states in the processes of the DNA-protein recognition are the consequence of the large-amplitude motions leading to the expression scenario [13]. Mesoscopic description of open complexes assumes the definition of internal "mesoscopic" variables reflecting the coherent behavior of the "minimal molecular set" of the breaking of the H-bonds. This set is close to 50 genes linked to the level of perturbation needed to trigger a multiscale spatial-temporal transition in the system [14]. The ensemble of "minimal set", associated with the open complexes, are responsible for the "structural memory" and realization of the cell plasticity, the cell damage, pattern formation, morphology and the shape fractality [10]. The open complexes as a typical mesoscopic defects are associated with the local unwinding, opening of the double helix. Biological processes involve ensembled molecular components (open complexes) responsible for mesoscopic properties, spatial-temporal multiscale organization according to epigenetic (thermodynamic) landscape in which system's transitions are realized [15]. Thermodynamic aspects of the open states can

be considered as the key problem for the understanding of the DNA functioning. Statistical approach to describe the collective behavior of the DNA distortion modes allowed the formulation of thermodynamics of the open complexes and the evolution equation in the generalized Ginzburg-Landau form reflecting specific type of criticality named as the structural-scaling transition [9]. Structural parameters associated with open complexes and corresponding localized untwisting modes were introduced as the localization of the symmetry group of distortion tensor. The microscopic parameter S_{ik} that is associated with the open complex represents the local distortion spreading on the small segment $2d$ (about 50 base pairs) with the opening normal distortion mode $\vec{B} = B\vec{V}$ to the segment area $\vec{S}_d = S_d\vec{V}$ $(S_d \sim \pi d^2)$ with orientation $\vec{V}$. The mean value of the open complex for uni-axial case $p = \langle s_{ik} \rangle$ corresponds to the minimum of the out-of-equilibrium free energy in the Ginzburg-Landau form

$$F = \tfrac{1}{2} A(1 - \delta/\delta_*) p^2 - \tfrac{1}{4} Bp^4 + \tfrac{1}{6} C(1 - \delta/\delta_c) p^6 - D\sigma p + \chi(\nabla_l p)^2 \quad (1)$$

where σ is the external constraint. The value of δ is the second structural parameter and represents the ratio of two characteristic scales $\delta=(d/l)^3$ the length d *(d~30-50nm)* of the DNA segment of open complex nucleation and the distance l between open complexes. The bifurcation points $\delta_*=1.3$, $\delta_c=1$ separate qualitative different areas of the free energy non-linearity: transition from the uni-modal to the bimodal form at $\delta_*=1.3$ with qualitative changes of the metastability at $\delta_c=1$ from the finite to the infinite depth of the second minima). The δ - parameter and the critical values $\delta_*=1.3$, $\delta_c=1$ play the role that is similar to the characteristic temperatures in the Ginzburg-Landau theory. The gradient term in (4) describes the non-local interaction in the distortion field; *A,B,C,D* and χ are the phenomenological parameters.

The Ginzburg-Landau free energy as the epigenetic landscape

The state space of the cells is related to the 'epigenetic landscape' due to 'causal interactions between genes and their products, which bring the phenotype into being' [11, 16, 17]. An epigenetic landscape can be interpreted as a free energy profile based on the entire ensemble of simultaneous interactions having the number for simple organism the order of 10^{7200}, that could be reconstructed to introduce on the scale of DNA the meaningful mesoscopic variables. The idea of an 'epigenetic landscape' was proposed by Waddington [18, 19, 20] as the sequence of the valleys with the free energy minima in terms of the variables reflecting the coherent gene-by-gene behavior. These variables can significantly affect nonlinear processes, thus switching cells between distinct phenotypes, by analogy with phase transition in physical systems [21]. Collective behavior of these variables (collective modes) could provide the reprogramming of cell states, that could be not realized by interactions between genes due very high kinetic barriers of the epigenetic landscape [22,23]. The energy profiles could be considered in the framework of the Ginzburg-Landau free energy using the internal variables reflecting the coherent gene-by-gene behavior as the expression unit related to the open complex. The flatness of epigenetic landscape under transition from unimodal to bimodal energy profile is the sign of the critical point, where the sharp increase of the relaxation time corresponds to the development of a global phase transition in the whole gene expression profile (the mRNA expression [14]) with the shift in the frequency profiles to the coherent mRNA expression modes. According to these results the critical dynamics of gene expression shows the singularity induced scaling that is characteristic for out-of-equilibrium critical systems. The open complexes and the mRNA coherent expression modes appear due to the decomposition of the free energy metastability. This metastability has different nature for corresponding ranges of the "governing" structural-scaling parameter transforming the unimodal potentials into bimodal potentials with finite and infinite depth depending on the δ - range [10].

Globally convergent dynamics of gene expression as an attractor states

Temporal development in gene-expression collective modes was studied to analyze the expression groups sorted according to normalized root-mean-square-fluctuation (*Nmsf*) and related to an early response (the first 30 min) to growth factors in a MCF-7 breast cancer cell population [22, 23]. The averaged values of *Nrmsf can be considered* quantitative as relationship with the mRNA expression. The hill-like distribution function marks a dynamical stable profile of expression

that in turn is defined as coherent expression state for a set of genes. As the consequence, it was assumed that *the nrmsf* can be considered as the order parameter for gene expressions stems with consolidated gene expression scales. It was noted [22] that the *nrmsf* should be related to the physical plasticity of genomic DNA: a higher nrmsf should be associated with a more pliable DNA structure. *Nrmsf* , as the spatial/temporal variance, should correspond to the degree of fluctuation/freedom in statistical thermodynamics. The log-normal law and the power law that are characteristic for the critical scenario, could link chromatin aggregation and gene expression as coordinated transitional behaviors at the chromosome level with coarse grain dynamics. Kinetics for the open complex parameter can be presented by the evolution equations for mentioned structural variables [10]:

$$\frac{dp}{dt} = -\Gamma_p \frac{\partial F}{\partial p}, \qquad \frac{d\delta}{dt} = -\Gamma_\delta \frac{\partial F}{\partial \delta}, \qquad (2)$$

where Γ_p and Γ_δ are the kinetic coefficients. The path of the bifurcation point δ_* leads to penetration into the metastability area and the generation of the collective finite-amplitude distortion modes with breather ($\delta \to \delta_*$) and solitary wave ($\delta_* > \delta > \delta_c$) dynamics (Figure 2).The solitary wave solution has the form $\rho(\zeta)=\rho(x - Vt)$, where the wave amplitude, velocity and the width of the wave front are given by the self-similar solution:

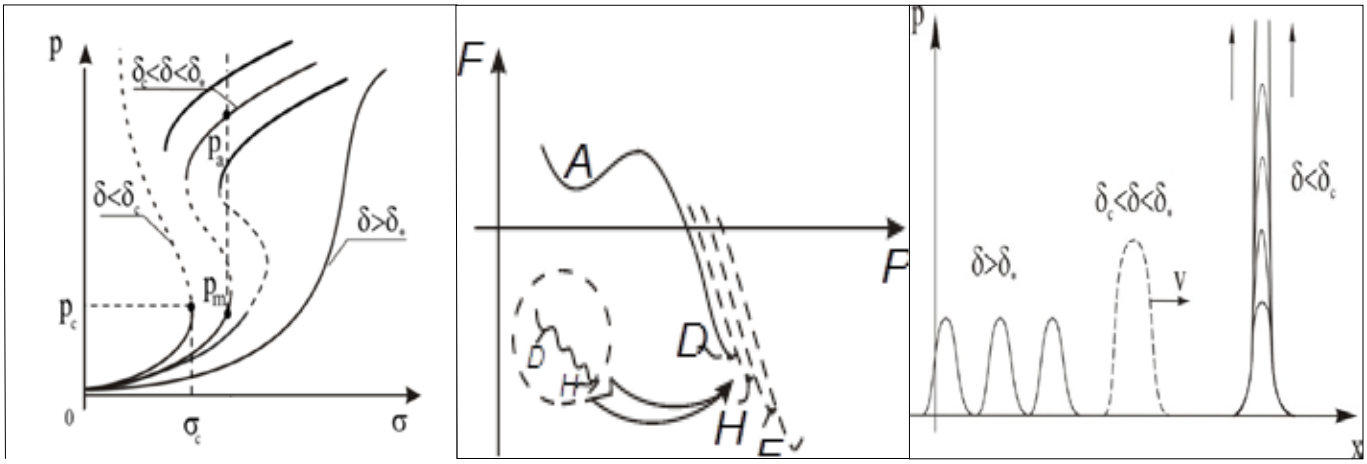
$$p = \frac{1}{2} p_a \left[1 - tahn\zeta\ L_{B^{-1}}\right], \quad L_B = \frac{4}{p_a}\left(2\frac{\chi}{A}\right)^{1/2} \qquad (3)$$

The velocity of solitary wave is $V = \chi A(p_a - p_m)/2\zeta^2$, where $(p_a - p_m)$ is the p-jump in the metastability area. A transition through the bifurcation point δ_c leads to the qualitative change of the double-wall potential into the form with infinite second minimum depth. These qualitative changes in the metastable potential lead to specific open complex dynamics, generation of collective distortion modes with "blow-up" kinetics [9].

Specific type of self-similar solution determines the kinetics of distortion modes for $t \to t_c$ on the set of spatial scales $L_H = kL_c, \quad k = 1,2,...K$:

$$p(x,t) = \varphi(t)f(\zeta), \quad \zeta = \frac{x}{L_c}, \quad \varphi(t) = \Phi_0\left(1 - \frac{t}{t_c}\right)^{-m} \qquad (4)$$

where $m > o$, $\Phi_o > o$ are the parameters related to the nonlinearity of free energy release in metastability, L_c and t_c are spatial and temporal parameters of "blow-up" self-similar solution. The existence of the set of collective modes and consequent transformation of these modes according to the δ- kinetics from the breather to solitary and blow-up dynamics illustra-



A B C

Figure 2: A - Phase diagram of open complex parameter p versus external constraint σ ; B – Free energy "epigenetic" landscape; C – Self-similar solutions corresponding to breathers (S_1), solitary wave (S_2), blow-up (S_3) attractors.

tes the globally convergent open complex dynamics in the presence of three different attractors, Figure 2. The value of structural-scaling parameter reflects the current susceptibility of the DNA ensemble to the nucleation and growth of the open complexes in the presence of the DNA constraint and the thermal bath. The kinetics of structural-scaling parameter provides the scenario of the spinodal decomposition in different areas of metastability due to the initiation of the open complex collective modes. These modes represent three types of the self-similar solutions of the evolution equations (2) for the open complex parameter p in characteristic areas of structural-scaling parameter: breathers, autosolitary waves and blow-up dissipative structures. The phase spaces of these attractors are linked to the sets of mentioned collective modes. The sets of collective open complex modes (breathers, solitary and blow-up modes), that could co-exist generally in the DNA double helix structure, represent the collective variables subject the non-linear dynamics of out-of-equilibrium biological system to a few preferred global states. The solutions (3), (4) have the nature of the self-similar intermediate asymptotic that allows the consideration of mentioned collective modes as the eigenfunction spectrum of nonlinear problems [9,24,25] that explains the gene expression as the resonance pattern forming without modification of the DNA's sequences [26]. The "evolution arrow" follows from the kinetics of structural-scaling parameter δ that realizes the natural tendency for transformation of breather and solitary modes into the blow-up modes. The interpretation of biological regulation within the framework of nonlinear dynamics of open complexes can be linked to the driving factor of the δ - kinetics providing the evolution pathway though the areas of different attractors to realize the gene expression scenario and the cell evolution [27]. This analysis demonstrates temporal development of gene-expression as global phase transition [28, 29, 30]. The robust organization in cells, when the expression mechanism of thousands of genes are coordinated by a few key transcription factors can be linked to attractor states in the gene-expression landscape [31, 32, 33] providing the 'phenotypic states'. The attractor concept envisages the system as evolving toward a preferred (minimal energy) state due to appearance of 'globally convergent' solutions [34, 35, 36, 37]. These solutions attract the system dynamics in the presence of stochastic fluctuations related to a gene-by-gene interaction. Attractor states are realized in the presence of a rugged non-equilibrium free energy landscape in the terms of mentioned variables as the generalization of the Landau theory of the phase transitions [38, 39].

The generalization of the Landau theory for thermodynamics of the DNA ensemble was developed in [10] using the "effective field" approach by Leontovich [40] for the statistical thermodynamics of the out-of-equilibrium "slow driven systems". In the presence of the free energy metastability (1) the $\boldsymbol{\delta}$ kinetics plays the role of the "intelligent agents" (Maxwell's demons) that used to drive the system due to the metastability decomposition [41]. This scenario could clarify a fundamental question concerning the problem of cell dynamics controlling genome-wide expression - What is the 'driving force' that attracts the entire system toward a few preferred global states, thus making the genome act as a single integrated system? [42, 43].

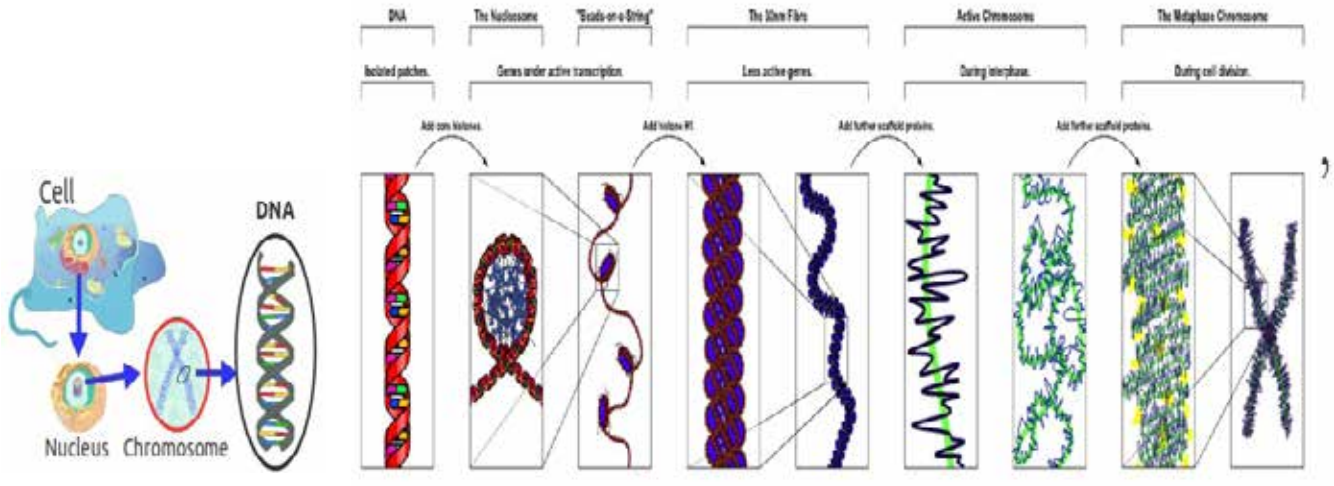


Figure 3: Cell structure and DNA transformation: A - cell structure, B - histone topology, C - histone package, D - cell division [https://en.wikipedia.org/wiki/Chromatin#/media/File:Chromatin_Structures.png].

The sequence of generation of these modes can be used for the explanation of the DNA transformation associated with the cell plasticity and the cell division, Figure 3 [44]. The front of autosolitary wave mode has the sharp curvature $\chi = (\partial p / \partial s)_f$ (s is the longitudinal DNA axis) separating the portions of DNA strands with breather and autosolitary wave dynamics that can be associated naturally with transition to the histon topology of the DNA strand (Figure 3a) in the condition of continuously increasing curvature along the s-axis under $\delta \to \delta_c$.

The solitary wave dynamics of the open complexes provides the active transcription action caused by the DNA plasticity and the meeting point (centromere) of two strands with inverse curvature can be considered as analogue of "sitting dislocation" with the high energy barrier. Double helix becomes more condensed due to the histon topology dynamics. Numerous scenario of the histone topology lead to the DNA package ("histone lattice", Figure 3b, c) with less active genes and new correlation in the open complex ensemble providing the path of the δ_c critical point. It leads to the excitation of blow-up open complex dynamics inside of histone topology, rupture of the DNA strands and the formation of small p chromosome arms (Figure 3d) as the precursor of the cell division [45]. The chromosome consists of the condensed structure of the DNA double-helix (10,000 times than in the normal DNA double-strand). The compact form of chromosomes has four arm structure as a pair of sister strands attached by each other at the centromere. The long q - chromosome arms appear due to the tripping of some labile histon stitching (centromere) with low energy barrier after the rupture of the DNA strands in histones. Finally, due to this act of replication a chromosome consists of two sister chromatids. The DNA transformation occurs in order for the proper separation of the genetic material between daughter cells under the cell cycle (Figure 3d). Similar scenario was discussed in [23] in early response to growth factors in a MCF-7 breast cancer cell population to characterize the distinct expression domains: static, transit and dynamic domains according to the degree of temporal variation in expression.

Laser Interference Microscopy of cell dynamics: ductile-brittle transition in CSK structure as cancer precursor

Open complexes as mesoscopic defects are responsible for two mechanisms in condensed matter associated with plasticity and damage-failure transition [44]. This is characteristic for the cells under the influence of physiological and pathological conditions through the qualitative transformation in the CSK structure. This transformation occurs as the sequence of critical events due to the path of critical points δ_* , δ_c in the attractors space. The breathers and auto-solitary modes are responsible for the cell plasticity, which indicates mechanobiological properties reflecting the natural CSK transformation and the transition to the third attractor with the phase space related to the blow-up collective modes providing the cell differentiation dynamics. This scenario of collective modes transformation reflects the duality of the open complex dynamics in the ductile-brittle CSK cycle. The structural-scaling transition events occur in the presence of the δ kinetics as the spinodal decomposition of the metastable free energy release caused by the dynamics of the open complex parameter considering the open complexes as mesodefects ensemble. The qualitative different robust statistics (the log-normal and the power statistics), is characteristic for ductile and brittle behaviors can be used for the identification of the normal and cancerous CSK states [46]. The CSK cycle of the normal cells is associated with spatial-temporal distributed collective modes of open complexes, which follow to the multifractal dynamics associated with mentioned attractor types and the log-normal statistics of finite amplitude open complex fluctuations. This stochastic multiplicativity of open complex dynamics from the breathers to auto-solitary and blow-up modes provides the evolutionary "ductile" stability of the normal cells up to the stage of the cell division. The qualitative different scenario is observed for the cancer cells with pronounced "brittle" dynamics leading to the power law statistics that is characteristic for self-organized fragmentation [47] and anomalous cell fragility for the arbitrary constraint. The cancer cell behavior can be linked to the activity of the third attractor $\delta \to \delta_c$ under the initiation of the convergent multiscale "blow-up" dissipative structures subordinated entirely the CSK dynamics. The study of the cell dynamics as the optical thickness fluctuations were conducted at

the Perm Federal Research Center of the Urals Branch of the Russian Academy of Sciences using the MIM-340 Laser Interference Microscope. Study of the nonlinear CSK dynamics using the data of the Laser Interference Microscopy (LIM) is the impact opportunity for the objectification of the cell states and cytological cancer diagnosis analyzing the time series of phase thickness fluctuations (in the "cross-sections" of the nucleus, the nucleolus, cytoplasm). The main advantages of the MIM-340 laser microscope are high resolution in the lateral plane (10-100 nm) and vertical (0.3 nm), the frequency recording of phase images (33 Hz) and the presence of an object table that allows the positioning the object (positioning accuracy is 150 nm) [48].

The results of typical measurements are presented in Figure 4 [49, 50, 51]. In these figures, the adhesion region of living cells (green color), a thin layer of cytoplasm (yellow color), nuclei (red color) and nucleolus (dark red color) are clearly visualized. High spatial and temporal resolution of the LIM pattern allowed the analysis of dynamic processes in living cells using LIM track diagrams in different cell cross-sections (Figure 5, 6). Optically dense area corresponds to the cell nuclei. These data were obtained by laser interference microscopy on 450 non-cancerous and cancer cells.

Wavelet transform maximum modulus method (WTMM) [52,53,54] was used to analyze the LIM data (Figure 5, 6) and to establish the correlation between the finite amplitude temporal fluctuation of the phase thickness (associated with the cell thickness in the nucleus cross-sections) and qualitative different CSK dynamics providing the cell plasticity and fragility. 1D realization of the WTMM method was used to process the LIM data, that allowed one to get the singularity spectrum $f(\alpha)$ corresponding to the mono- and multifractal dynamics (Figure 7) [27,50,51]. Both scenarios

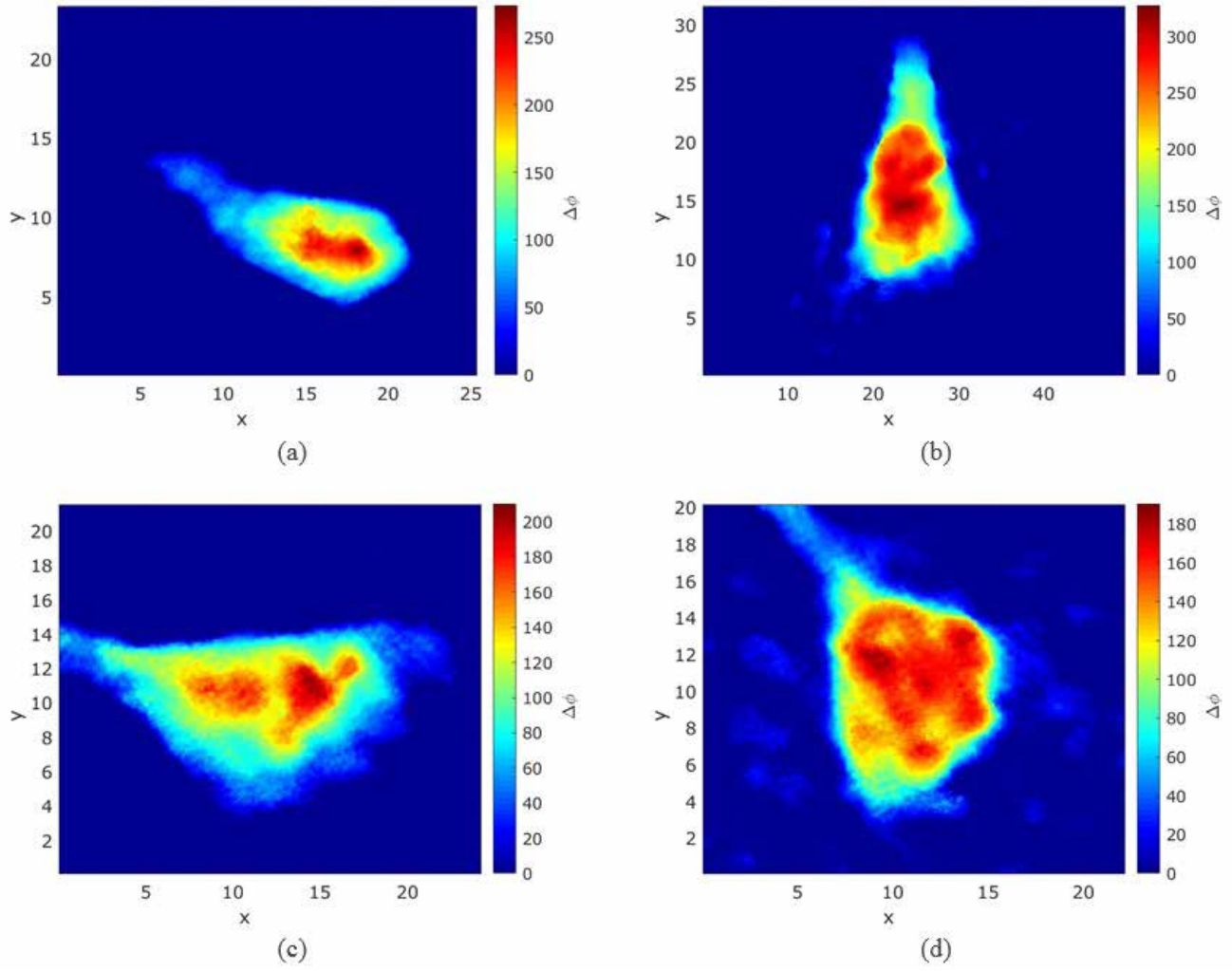


Figure 4: Phase images of the cells: (a) MCF-7, (b) HEK 293, (c) MCF-7, (d) HCT116. Units of measurements: x, y – mkm; ΔΦ – nm.

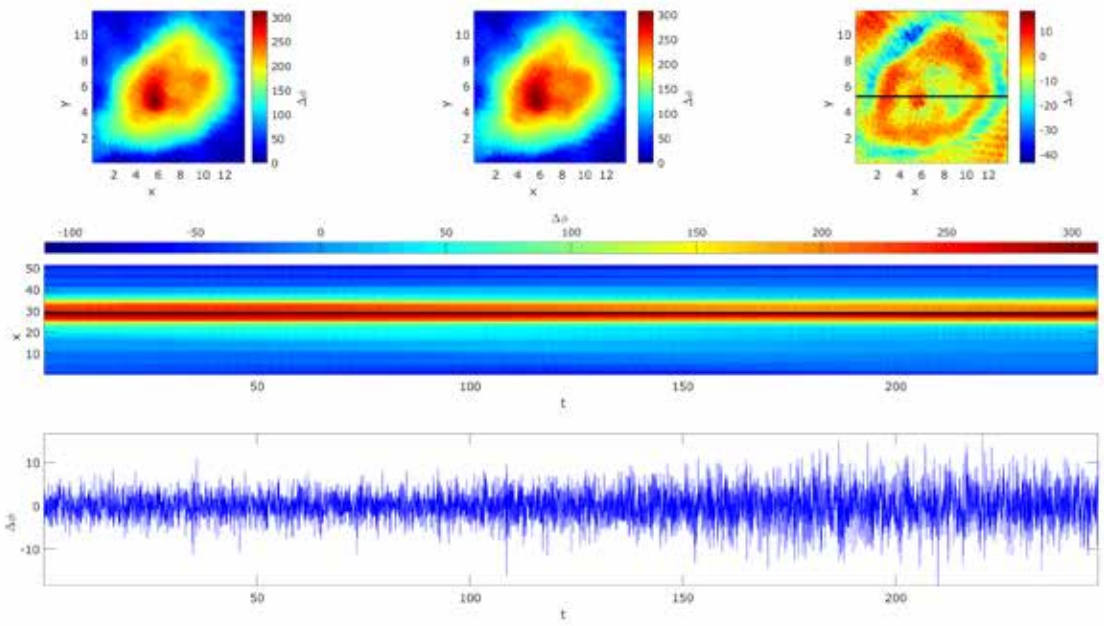


Figure 5: Typical phase images registered at different time, difference frame, track diagram and 1D signal of the normal human breast epithelial cell MCF-10A. Units of measurements: x, y — mkm ΔΦ — nm.

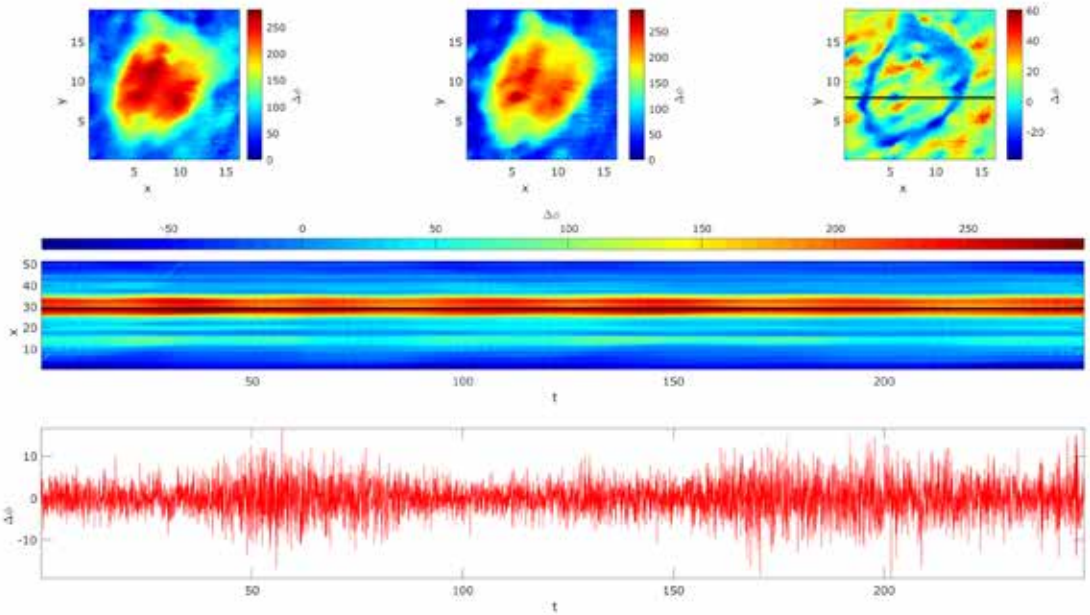


Figure 6: Typical phase images registered at different time, difference frame, track diagram and 1D signal of the cancer human breast epithelial cell MCF-7. Units of measurements: x, y — mkm ΔΦ — nm.

display fat-tail distributions (log-normal and power laws) that are characteristic for the critical systems dynamics subject to the collective modes providing the spinodal decomposition of free energy metastability (free energy release) [46,47, 54]. The log-normal multiplicative statistics reflects the influence on the CSK dynamics the mentioned types of collective modes in the course of the normal cell evolution as the structural-scaling transition in the open complex ensemble. The power law statistics reflects the cell fragility that is the

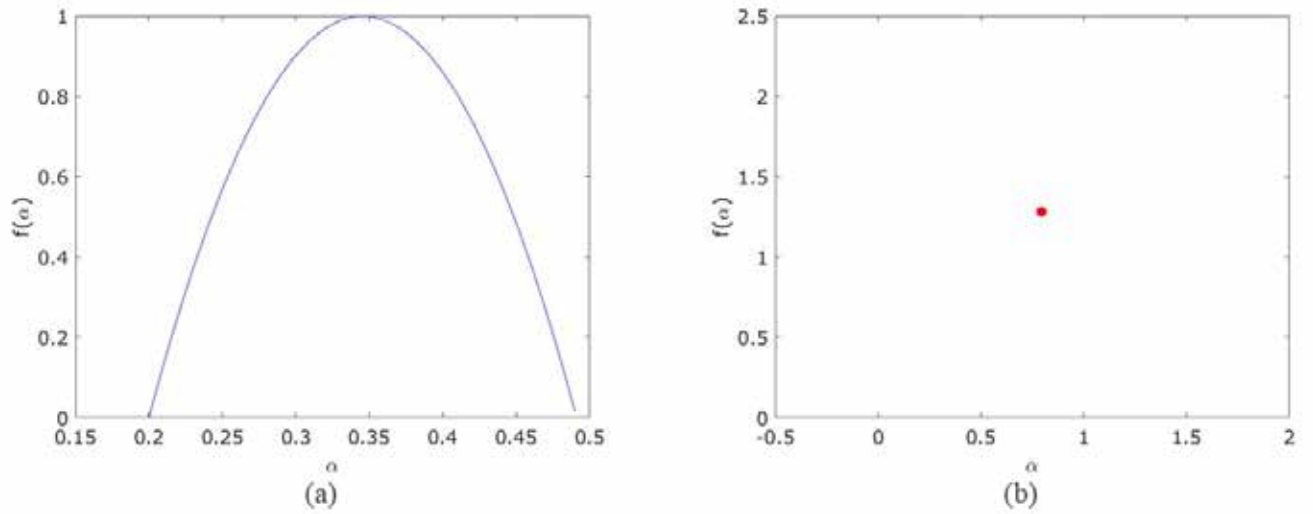


Figure 7: Typical multifractal spectra of LIM data: "blue" is the normal breast cell, "red" is the cancer breast cell (carcinoma).

consequence of pathological structural changes (corresponding to the range of structural-scaling parameter $\delta<\delta_c$) leading to the subjection of the CSK dynamics to multiscale blow-up modes. These results allow the conclusion concerning the duality of multiscale open complex dynamics responsible for the evolutionary cell transformation as the ductile structural-scaling transition in the cell division and the brittle dynamics leading to the cell fragility and the cancer development.

Entropy: convergent and divergent cell dynamics

The structural-scaling transitions in nonlinear out-of-equilibrium systems are characterized by dynamically unstable motions in the terms of an exponential divergence on initially adjacent trajectories [55]. The measure of exponential divergence is the Kolmogorov-Sinai entropy (or the so-called K-entropy). The K-entropy is related to the average rate of divergence of initially adjacent trajectories $x_i(k)$ and hence the Lyapunov exponents λ_i

$$K = \sum_i \lambda_i , \quad \lambda_i > 0 \tag{5}$$

Instead (5) the K-entropy can be introduced as the characteristics of dynamic divergence $D(k)$ of the trajectories $x_i(k)$ [56]

$$K = \lim\left[\frac{1}{n}\sum_{i=1}^{n} \ln \frac{D(k)}{D(0)}\right], \quad D(k) = \left[x_1(k) - x_2(k)\right] \tag{6}$$

as the average time of the current trajectories divergence k to the initial one. If we introduce the corresponding probability distribution of the trajectory divergence at the point in time t

$$f(D, t), \quad \int f(D, t)dD = 1,$$

the entropy of the system can be defined as

$$S(t) = \int 1n\, f(D, t) f(D, t)dD\,. \tag{7}$$

The distribution $f(D, t)$ can be used to introduce two characteristics of the system dynamics: an average divergence at the point in time t and the effective "volume" of the divergence

$$D(t) = \int D f(D,t)dD, \quad \Delta D(t) = \frac{1}{f(D,t)} \tag{8}$$

With small deviation of $\Delta D = D - \overline{D}$ from the average value $\overline{D}$, the entropy (7) can be determined by the analogue of the Boltzmann formula

$$S(t) = 1n\, \Delta D(t). \tag{9}$$

Using (6) and (9) we can find two equivalent relations:

$$S(t) - S(t_0) = \ln \frac{\Delta D(t)}{\Delta D(t_0)}, \quad \Delta D(t) = \Delta D(t_0)\exp\left(S(t) - S(t_0)\right), \tag{10}$$

The latter definition can be considered as the analogue of the uncertainty relation: the large trajectory divergence has the higher entropy. Using (10) the statistical analogue of the *K*-entropy can be introduced as the average rate of the entropy change in a time $(t-t_o)$

$$K_{stat} = \frac{S(t) - S(t_0)}{t - t_0} = \frac{1}{t - t_0} \ln \frac{\Delta D(t)}{\Delta D(t_0)} \qquad (11)$$

It follows from (11) that k_{stat} determines the entropy production averaged over a finite time interval. Local entropy change reads as the entropy balance equation

$$\frac{dS}{dt} = \frac{d}{dt} \ln \Delta D(t) = \sigma(t) \qquad (12)$$

It is seen that the entropy production has not fixed sign and increases or decreases as the average trajectory divergence.

Development of collective open complex modes (breathers, auto-solitary, blow-up) is the consequence of the local instability due to the subordination of the cell dynamics to the set of the self-similar solutions. Singular nature of the open complex as defects allows the consideration of open complex collective modes as the string objects [25] with the interactions responsible for dramatic change in the symmetry properties and the transformation pattern in Figure 3. The first symmetry breaking occurs in the course of mutual excitation of the breathers as the expression template related to the epigenetic landscape. The scale renormalization in the breather ensemble provides the long range correlation in more coarser epigenetic landscape, the second symmetry breaking due to the metastabilty decomposition in the range $\delta_* > \delta > \delta_c$ with the generation of auto-solitary modes and realization of the transcriptional dynamics, the histone topology and the histone package. The scaling related to the auto-solitary modes leads to the second bifurcation at $\delta = \delta_c$ eading to the generation of blow-up open complex modes providing the cell division scenario. This pathway of the normal cell evolution occurs in the presence of three attractors excited consequently due to the structural-scaling transition and the convergence of trajectories related to the open complex dynamics of mentioned collective modes. As the consequence, this dynamics is characterized by the minimum of the entropy production. The multiply "resonance" excitation of the third blow-up attractor localized on the set of the fundamental lengths L_k is characteristic for the cancer cells revealing the divergent dynamics and the spontaneous fragility. The resonance excitation of the multiply blow-up modes is typical for the epigenetic landscape with pronounced coarsening of the metastable potential in the presence of the infinite second minima. The mutual resonance blow-up kinetics of the open complexes leads to the spontaneous DNA fragmentation and low viscosity that is observed for the strongly coupled systems [25]. The low viscosity could provide the anomalous proliferation as the metastasis mechanism.

Conclusion

The mechanobiology of living cells is associated with the cytoskeleton (CSK) dynamic network (filamentous proteins, actin filaments, microtubules, intermediate filaments) revealing the fundamental property of the cells qualified as the cell plasticity and the cell damage. Plasticity is the phenomenon inherently linked to the collective behavior of mesodefects in the "biological crystals" (the open complexes in the DNA double helix) and provides the unique mechanism of the defects induced momentum transfer and the structural memory as the expression scenario. The cell plasticity can be considered as the leading mechanism providing the vital CSK properties, including the DNA transformation, expression dynamics, the cell division. Open complex mechanisms of plasticity and fragility are analyzed as specific type of critical phenomena in condensed matter with mesodefects – the structural-scaling transition. The expression dynamics, the self-organization of DNA and the cells are linked to the collective modes of the open complexes (breathers, auto-solitary waves, blow-up dissipative structures) responsible for the configuration mobility of the CSK structure and the cell division. The gene expression and the cell division being the vitality ground have natural links to the defects behavior and provides the evolutionary meaningful mechanisms of self-organization for normal cell dynamics or pathological scenario of defects induced fragility as the cancer precursor. Study of the nonlinear CSK dynamics was conducted analyzing the time series of phase thickness fluctuations after the Laser Interference Microscopy in the cell "cross-sections" containing the nucleus, the

nucleolus, cytoplasm. The application of the WTMM method allowed the demonstration of the links of temporal correlations of finite-amplitude phase thickness fluctuation, dynamics of collective modes of open complexes and qualitative different CSK dynamics that are characteristic for the cell plasticity and fragility. The phase thickness fluctuations display the fat-tail distributions, the log-normal and the power laws, with multi- and monofractal singularity spectrum. The multifractal singularity spectrum in the case of the cell plasticity reflects the temporal sequences of the phase thickness fluctuation in the presence of mentioned open complex "singular" collective modes (breathers, auto-solitary, blow-up). The monofractal singularity spectrum and the power law of the phase thickness fluctuation are the consequence of the shifting of the CSK dynamics into the area of the attractor with the blow-up open complex dynamics, that leads to the spontaneous CSK fragmentation (the cell fragility). The open complex dynamics, which follows to the structural-scaling transition, allows the interpretation of the normal and cancer cell evolution scenario. The structural CSK susceptibility to both scenario is given by the values of structural-scaling parameter charactering the nonlinearity (metastability) of the epigenetic landscape and corresponding open complex kinetics. The pathological changes of the CSK structure in the presence of the "monofractal" blow-up open complex dynamics leads to the cancer progression.

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