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Survival at Tumor Recurrence in Soft Matter

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Abstract

Survival at tumor recurrence in soft matter, after chemotherapy, is assessed by RNA folding. It is shown that this recurrence is starting with development of a fluidlike globule; it changes the energy of soft matter; it proceeds as a resonant mixing; and at the end it causes diffusion. This diffusion is interpreted as metastasis in soft matter. A tumor memory is designed for its recurrence oscillations. These oscillations are marked as positive or negative according to their influence on life stabilization or destabilization. It is demonstrated that a tumor memorizes two types of recurrences. The intensity of chemotherapy in soft matter for a tumor with such memory is obtained. Survival at tumor recurrence in soft matter, after chemotherapy, is assigned to one of the five regions of the phase diagram of the "thermalized" tumor by microenvironment. To each of these regions is collated a breast cancer survival class. It is found that the survival at tumor recurrence in soft matter, after chemotherapy, well represents actual survival of 32 patients with breast cancer.

Keywords

Survival, Tumor Recurrence, Life Stabilization, Chemotherapy, Soft Matter

1. Introduction

Macromolecules are influenced by different long-distance fields of nature, such as gravity and electromagnetism, in addition to the intrinsic vibratory states of macromolecules that locally generate coherent excitations in the cell [1] [2] [3]. DNA and protein folding, in a biological evolutionary context, may be guided [2] by a set of discrete electromagnetic frequency bands that either promote or inhibit carcinogenesis. Therefore, the tumor recurrence, after chemotherapy, can be considered as evolution of gravitating quantum matter and represents tumor recurrence in soft matter. This is system's oncology consideration [4] [5] of tumor recurrence, after chemotherapy.

Survival at tumor recurrence, in soft matter, for the above embedding of DNA and proteins in integral cellular context, after tumor chemotherapy, is investigated in this paper. That's why the tumor recurrence in soft matter will be studied using the transition [6] from unfolded state into a folded state of the human telomerase RNA pseudoknot upon a jump in the ion concentration (ion-jump) and temperature-quench. In addition, chemotherapy is defined as a probability of success, transferred chemical energy and restoration time.

2. Folding State

Folding state of human telomerase is [6] like a low-energy fluidlike globule. Let the folding state is a fluidlike globule, which is a protein aggregation with fission.

The process [7] of protein aggregation with fission is with Weibull-type limiting distribution. Then the probability of such a protein cluster p_a is found from the probability of chemotherapy success p_s according to graphic by Jo *et al.* [7], when the Weibull-type distribution modules, defining this probability, are equal. The probability for a fluidlike globule occurrence is the probability for occurrence of such a protein cluster p_a.

Let δ_{ex} is the difference of the protein cluster probability p_a and the chemotherapy success probability p_s, $\delta_{ex} = p_a - p_s$. The time to reach the folding state, which is a fluidlike globule at tumor recurrence, τ_{ex} is obtained for the difference δ_{ex}, considered as open system quasiprobability [8] of single qubit in quantum non-demolition noise. Time τ_{ex} is obtained from the graphic in Thapliyal *et al.* [8] of the quasiprobability distribution that is a shifted P-function for a temperature, equals to one. Here the P-function is shifted so that its value to be zero in the initial moment.

3. Folding Kinetics

The human telomerase reaches [6] a folded state through a small number of connected clusters that are repeatedly visited during a pulse sequence in which the folding or unfolding is interrupted. These clusters are hidden states of RNA folding kinetics [6]. This folding kinetics is [6] with two sparsely kinetically connected channels that carry the flux to the folded state. Let the conformation of this two sparsely kinetically connected channels is the knot "Figure-Eight". Then the tumor recurrence in soft matter is characterized by the actual amplitude, connected [9] to Jones polynomial for the knot "Figure-Eight". This actual amplitude is found for the difference of the phase shift θ, after the chemotherapy, of the state in soft matter and the phase shift $\pi/4$ of the maximally coherent state, according to the graphic from Schulte-Herbrüggen *et al.* [9]. Here the phase shift θ is obtained [10] from the restoration time τ_r,

$$\theta = \arccos\left(v_r^2\right),\ v_r = 20/\tau_r . \tag{1}$$

In Equation (1) v_r is the recovery speed at chemotherapy in soft matter.

Time for RNA folding upon ion-jump $\tau_{f,1}$ is obtained from the graphic by

Biyun *et al.* [6] for a square root from the above mentioned actual amplitude, taken with a negative sign. Here is assumed that a square root from the above mentioned actual amplitude, taken with a negative sign, gives the fraction of molecules that remain folded upon ion-jump.

Similarly, the time for RNA folding at a temperature-quench $\tau_{f,2}$ is found from the graphic by Biyun *et al.* [6] for a square root from the above mentioned actual amplitude, with a negative sign. Here again is assumed that a square root from the above mentioned actual amplitude, taken with a negative sign, gives the fraction of molecules that remain folded at temperature-quench.

Let δ_f is the time difference for RNA folding at temperature-quench $\tau_{f,2}$ and the time for RNA folding upon ion-jump $\tau_{f,1}$, $\delta_f = \tau_{f,2} - \tau_{f,1}$. This difference is positive because the rate of human telomerase compaction is [6] greater when folding is initiated by ion-jump than by temperature-quench. Then, similarly to the uncertainty principle, the minimal energy change at tumor recurrence in soft matter as a quantum-classic transition δE and the time difference δ_f can be linked like that

$$\delta E = 1/\left(2\pi\delta_f\right). \tag{2}$$

4. Resonant Mixing

Periodically interrupted RNA folding, upon ion-jump and temperature quench, can be considered as a resonance of a relay relaxation oscillator [11], under periodic external forcing due to the presence of stretching and folding action. Here the relay relaxation oscillator consists of relay hysteresis and an integral feedback, where the periodic external forcing is at the input of the integrator.

Let the normalized autonomous period of the considered oscillator σ is equal to the time for quantum-classical transition of the tumor recurrence τ_{ex}, $\sigma = \tau_{ex}$. Here the normalized autonomous period σ is the ratio of the natural half-period of the relay relaxation oscillator and the half-period of the periodic external forcing T.

Let ε is the amplitude of the periodic external forcing, and θ_1 is the phase at the first switching. Then [11], if $\left\{2+(\varepsilon-1)^2/(\varepsilon+1) < \sigma < 2+(\varepsilon-1)^2/2\right\}$ the oscillator is entrapped at the primary harmonic with a period 2T when θ_1 is in the interval $\left[0,1-2(\sigma-2)/(\varepsilon-1)^2\right]$ or in the interval $\left[(\sigma-2)/(\varepsilon-1),1\right]$. Here the "oscillator is entrapped" in sense that its initial phase lies in the domain of attraction of the resonance state. This oscillator is [11] in a resonant mixed mode.

Then RNA folding, upon ion-jump and temperature quench, is entrapped by the primary harmonic with a period $2T$, $T = 10$, if σ fulfils the above σ-condition and if the phase shifting θ of the state in soft matter, after chemotherapy, is the phase at the first switching $\left(1-2(\sigma-2)/(\varepsilon_1-1)^2\right)$ or $\left((\sigma-2)/(\varepsilon_2-1)\right)$. In this case, the amplitude of the tumor recurrence is ε,

$$\varepsilon_1 = 1+\left(2(\sigma-2)/(1-\theta)\right)^{1/2},\ \varepsilon_2 = 1+(\sigma-2)/\theta. \tag{3}$$

5. Tumor Recurrence Metastasis

Tumor metastasis is triggering the tumor recurrence in soft matter through resonant mixing for RNA folding upon ion-jump and temperature quench. Let the tumor recurrence is evolution of gravitating quantum matter, proceeding as nonlinear evolution of weakly perturbed anti-de Sitter space. Then [12] the tumor metastasis in soft matter can be observed as the onset of weakly turbulent instabilization under some arbitrarily small generic perturbations. This metastasis gives rise to [12] diffusion of energy from the low frequencies to high frequencies.

It follows [12] that the tumor recurrence, in soft matter, turns into metastasis in the very moment, when the onset of instabilization is observed. That's why the tumor recurrence in soft matter turns into metastasis in the moment t_1, $t_1 = 20/\varepsilon_1^2$, or in the moment t_2, $t_2 = 20/\varepsilon_2^2$.

6. Oscillations at Tumor Recurrence

Let tumor recurrence in soft matter is a quantum-classic transition with an initial state that is a highly quantum state. Then [13] the gravitating quantum matter in such an initial state tends to "decohere" towards the energy eigenstate with the highest energy. This tumor recurrence, in soft matter, grows into tumor metastasis in soft matter from §5.

Then the probability p_1, the state of the gravitating quantum matter in the moment $t_{n,1}$, not to be the same as its initial state, is [13]

$$\begin{aligned} &p_1 = \cos^2\theta \sin^2\left(\omega_{n,c} t_{n,1}\right),\ \omega_{n,c} = \left(2\pi/10\right)\omega_c, \\ &\omega_c = \left(E + \delta E\right)\sin\theta,\ t_{n,1} = 10t_1/\left(2\pi\right). \end{aligned} \tag{4}$$

Probability p_2, the state of the gravitating quantum matter in moment $t_{n,2}$, to be the same as its initial state, is [13]

$$\begin{aligned} &p_2 = 1 - \cos^2\theta \sin^2\left(\omega_{n,c} t_{n,2}\right),\ \omega_{n,c} = \left(2\pi/10\right)\omega_c, \\ &\omega_c = \left(E + \delta E\right)\sin\theta,\ t_{n,2} = 10t_2/\left(2\pi\right). \end{aligned} \tag{5}$$

In Equation (4) and Equation (5) θ is a phase shift from (1), E is the transferred chemical energy during chemotherapy in soft matter and δE is the minimal energy change at the tumor recurrence in soft matter from Equation (2). Here ω_c is the angular frequency of the oscillations of the probabilities from Equation (4) and Equation (5). This angular frequency is normalized so that the frequency $f_{n,c}$, $f_{n,c} = \omega_{n,c}/\left(2\pi\right)$, to be equal to photo reduction with "10" angular frequency ω_c, $f_{n,c} = \omega_c/10$. Simultaneously are normalized times t_1 and t_2, so that the probabilities p_1 and p_2 not to be changed. New times $t_{n,1}$ and $t_{n,2}$ are with the size of the recovery time τ_r.

7. Marker of Life Stabilization

Viability of life systems is affected [1] [2] by electromagnetic frequencies of tissues, cells and biomolecules, in the range from one-tenth of Hertz till Peta Hertz.

Stabilizing (beneficial) and destabilizing (detrimental) frequencies show repeated patterns of twelve bands and are positioned on two 12-number scales. These two scales, correspondingly, are a coherent scale for electromagnetic frequencies in Hertz (256.00, 269.70, 288.00, 303.41, 324.00, 341.33, 362.04, 384.00, 404.54, 432.00, 455.12, 486.00) [Hz] and non-coherent scale for electromagnetic frequencies in Hertz (249.41, 262.75, 278.71, 295.60, 313.51, 332.47, 351.54, 372.88, 394.12, 418.06, 443.41, 470.28) [Hz]. These scales and their self-similar extensions form octave hierarchies (Geesink and Meijer, 2018).

The above coherent scale for electromagnetic frequencies can be coarse grained to the following color scale: 1) blue-green (269.70, 288.00, 303.41) [Hz]; 2) green-yellow (455.12, 486.00, 256.00) [Hz]; 3) red (384.00, 404.54, 432.00) [Hz]; 4) violet (324.00, 341.33, 362.04) [Hz]. These four coarse grained colors approximately correspond to the colors of CdSe quantum dots [14] for diagnostics of cancer.

Life stabilization marker at tumor recurrence in soft matter m_s is defined by the frequency f_u, $f_u = 10^3 f_{n,c}$, from the interval diagram of beneficial and detrimental frequencies by Meijer and Geesink [2]. Here $f_{n,c}$ is the frequency from §6. Marker values of m_s are:

1) Positive, when the frequency f_u is the frequency, beneficial for life. This marker value is denoted by (+);

2) Negative, when the frequency f_u is the frequency, detrimental for life. This marker value is denoted by (−);

3) Undefined, when the frequency f_u is out of intervals of the beneficial and detrimental frequencies.

In correspondence with two octave hierarchies, the transition time from metastasis tumor state into protein aggregation state $t_{n,1}$ and the time for remaining into the state of metastasis tumor $t_{n,2}$, are measured in weeks.

8. Minimal Memory for Tumor Recurrence

Let the tumor recurrence in soft matter is near-random stochastic process that governs one-dimensional quantum Ising condensates chain. Each of these condensates plays the role of quantum spin. Here one-dimensional quantum Ising chain is a system of interacting quantum spins subject to the influence of a magnetic field. To this stochastic process corresponds [15] classical ε-machine with two causal states s_0 and s_1 and transition probabilities between them T_{ij}, $i, j = 0, 1$. Here T_{ij} is transition probability for the classical ε-machine of the process in state s_i to output $(-1)^j$ and transition to s_j.

This stochastic process possesses [15] an optimal quantum model with two pure states and maximal fidelity F,

$$F^* = \left(T_{00}T_{10}\right)^{1/2} + \left(T_{01}T_{11}\right)^{1/2}. \tag{6}$$

Two pure states of this quantum model are in one-to-one correspondence with classical causal states. Here the optimal quantum model is optimal over all quantum models.

This optimal quantum model is with a minimal memory, required for tumor recurrence modeling in soft matter. Because this model is quantum, it requires less memory than classical ε-machines.

Let the two casual states of the classical ε-machine of tumor recurrence in soft matter are:

1) Casual state s_0 of metastasis that is a state of protein aggregation at tumor recurrence;

2) Casual state s_1 that is a metastasis tumor state at recurrence tumor.

Let this classical ε-machine is with the following transition probabilities:

1) The probability of transition from the metastasis tumor state into a state of protein aggregation T_{10} is the probability p_1, $T_{10}(s_1 \to s_0) = p_1$;

2) The probability for remaining in a metastasis tumor state T_{11} is the probability p_2, $T_{11}(s_1 \to s_1) = p_2$;

3) The probability for transition from protein aggregation state into metastasis tumor state T_{01} is the probability of chemotherapy failure, $T_{01}(s_0 \to s_1) = 1 - p_s$;

4) The probability for staying in a protein aggregation state T_{00} is the probability for chemotherapy success, $T_{00}(s_0 \to s_0) = p_s$.

Then maximal fidelity of the tumor recurrence in soft matter is:

$$F^* = (p_s p_1)^{1/2} + ((1 - p_s) p_2)^{1/2}. \quad (7)$$

At such tumor recurrence, the transition from a metastasis tumor state into protein aggregation state takes time $t_{n,1}$ with a probability p_1, and staying in a metastasis tumor state is for time $t_{n,2}$ with probability p_2.

9. Types of Recurrence Development

Let metastasis is triggered by magnetic field of the upper quantum Ising chain, and protein aggregation is characterized by spin-spin correlations of the upper quantum Ising chain with a coupling parameter, equals to one. Then the recurrence development time is:

1) Tumor recurrence, where the metastasis is much weaker than protein aggregation;

2) Tumor recurrence, where the metastasis dominates over protein aggregation.

Statistical complexity of the tumor recurrence, where the metastasis is much weaker than the protein aggregation, is obtained by the graphic [16] for the statistical complexity of a quantum Ising chain with a system magnitude, equals to 9, as a ratio function of the magnetic field strength and the coupling parameter. Statistical complexity of this type recurrence is C_μ, when this ratio is equal to maximal fidelity F^* from Equation (7).

The fidelity F_d of recurrence, where the metastasis dominates over protein aggregation, is found from the graphic [16] for the statistical complexity of a quantum Ising chain as a function of the ratio of magnetic field strength and the coupling parameter, for statistical complexity C_μ.

10. Chemotherapy in Soft Matter

Let the chemotherapy protocol, at tumor recurrence in soft matter, is [17] that changes global properties of the tumor state by flipping a local switch. Here the switching of the local switch is a switching between RNA folding and RNA unfolding. Then the chemotherapy at tumor recurrence in soft matter can be determined as non-equilibrium time evolution after quench in quantum XY fermionic chain. This chemotherapy acts as staggered magnetization.

The intensity of this chemotherapy, at a transition from the metastasis tumor state into protein aggregation state $k_{s,1}$, is found from the graphic [17], as a staggered magnetization $B_1/10$ for a time $t_{n,1}/10$.

The intensity of this chemotherapy, while remaining at a state of the metastasis tumor $k_{s,2}$, is found from the graphic by Fagotti [17] as staggered magnetization $B_2/10$ for a time $t_{n,2}/10$.

When times $t_{n,1}$ and $t_{n,2}$ are less than 18 weeks, the intensity of this chemotherapy is found from the graphic by Fagotti [17] for times $\left(t_{n,1}+21\right)$ and $\left(t_{n,2}+21\right)$, correspondingly.

11. Survival at Tumor Recurrence

Survival at tumor recurrence in soft matter after chemotherapy is determined after interacting of the quantum model with a minimal complexity from §8 with tumor microenvironment. Let the tumor microenvironment "thermalizes" [18] this quantum model. Then survival at tumor recurrence in soft matter can be found from a ground-state phase diagram [18] of the one-dimensional axial next-nearest-neighbor Ising model in a transverse field with a system size, equals to 16. Let this system is with a transverse magnetic field B_x, ferromagnetic nearest-neighbor Ising coupling J_1 and antiferromagnetic next-nearest-neighbor interaction J_2. As well, it is assumed [18], that $J_1 = 1$ as the unit of energy.

Phase diagram [18] of this system is with a form of a fan with five sections. Each of these sections is a phase region, determined by the transverse magnetic field strength and antiferromagnetic next-nearest-neighbor interaction. These regions are:

1) Ferromagnetic phase (F_r);
2) Modulated phase (P_3);
3) Modulated phase (P_2);
4) Floating phase (P_1);
5) <2, 2> antiphase.

Here phase regions are numerated from left to right.

Let strength of a transverse magnetic field of this system is equal to maximum fidelity F^* from Equation (7), for tumor recurrence, where the metastasis is much weaker than the protein aggregation. Then, depending on the chemotherapy intensity, antiferromagnetic next-nearest-neighbor interaction is:

$$J_{2,1}=10k_{s,1}/F^*,\ J_{2,2}=10k_{s,2}/F^*. \tag{8}$$

Let the strength of the transverse magnetic field of this system is equal to fidelity F_d, for tumor recurrence, where the metastasis dominates over the protein aggregation. Then, depending on chemotherapy intensity, antiferromagnetic next-nearest-neighbor interaction is:

$$J_{2,3} = 10k_{s,1}/F_d\,,\ J_{2,4} = 10k_{s,2}/F_d\,. \tag{9}$$

Survival after tumor recurrence is determined according to:

1) Recurrence, where the metastasis is much weaker than protein aggregation. Then the survival region is determined by phase diagram [18], at a system size, equals to 16, for:

a) Transverse magnetic field strength F^* and antiferromagnetic next-nearest-neighbor interaction $J_{2,1}$, at a life stabilization marker $m_s = \{(+), \text{undefined}\}$;

b) Transverse magnetic field strength F^* and antiferromagnetic next-nearest-neighbor interaction $J_{2,2}$, at a life stabilization marker $m_s = \{(-), \text{undefined}\}$.

2) Recurrence development, where the metastasis dominates over protein aggregation. Then the survival region is found by the phase diagram [18], at system size, equals to 16, for:

a) Transverse magnetic field strength F_d and antiferromagnetic next-nearest-neighbor interaction $J_{2,3}$, at life stabilization marker $m_s = \{(+), \text{undefined}\}$;

b) Transverse magnetic field strength F_d and antiferromagnetic next-nearest-neighbor interaction $J_{2,4}$, at life stabilization marker $m_s = \{(-), \text{undefined}\}$.

12. Breast Tumor Survival

Survival for breast cancer patients is found in one of the following five classes:

1) Less than 36 months;

2) Between 36 and 60 months;

3) Between 60 and 90 months;

4) Between 90 and 126 months;

5) More than 126 months.

Let the survival of breast cancer patients corresponds to the survival at tumor recurrence in soft matter. Then for the breast cancer patients' survival can be concluded from the above phase diagram. This assessment can be found when the survival class with one number is compared to a region from the phase diagram with the same number. In this case the survival from tumor recurrence in soft matter is measured in weeks in correspondence with two octave hierarchies from §7.

Survival for breast cancer patients is assessed by making an assumption for the recurrence type; the patient's life stabilization marker is calculated; the chemotherapy for this type of recurrence is obtained; the survival region is determined; the patient's survival is classified in accordance with this region.

13. Results

Database is used for 424 patients with breast cancer, who were under treatment at the Clinic of Chemotherapy, National Oncology Medical Center, Bulgaria,

throughout 2003-2014. From them is randomly selected a group of 32 patients with different TNM staging (T-tumor size, N-lymph node status, M-distant metastasis), histology and imunohistochemic characteristics. For all patients the proliferation index has been tested. Research for gene expression has not been done. Their medical history is retrospectively tracked, their current survival is reported (March 2020) and is investigated a correlation with the standard clinical pathological criteria of risk assessment: TNM staging, histology, tumor differentiation grade, (ER, PR, HER2) receptor status. Patients with soft tissue sarcoma or other carcinomas aren't included in the group.

The probability of success, the transferred chemical energy and the restoration time are obtained from the proliferation index of the particular tumor via chemotherapy model in soft matter by Trifonova *et al.* [19].

Proliferation index (PI) estimates the expected time for tumour doubling. PI is assessed by immunohistochemical staining for detecting the proliferating cell nuclear antigen (PCNA). PCNA is a protein that is involved in DNA replication processes, which is found in the nucleus and is a cofactor of the DNA polymerases δ and ε. For PI reference value is accepted its value in a normal matter of 6%. As well, it is accepted that tumor recurrence, where metastasis is much weaker than protein aggregation, occurs with a proliferation index less than 51.01%.

Chemotherapy success, using the chemotherapy model in soft matter by Trifonova *et al.* [19], is not defined for five patients. These cases remain outside the present studies.

One patient is omitted from the study due to a lack of invasive component in the tumor at the subsequent revision.

The case studies with large discrepancies between the chosen survival class and the actual survival are six. In five of them the prognostic survival is assessed correctly and the discrepancy is due to a lack of disease stage in the model. For one patient with a moderate risk of recurrence and death the prognostic survival is overestimated.

Performed research demonstrates that in 25 cases from a total 26 cases (96.2%) there is a nearly coincidence between the chosen prognostic survival class and the actual survival, as well a correlation with the standard clinical pathological criteria of risk assessment.

Life stabilization at recurrence is undefined in two patients with identical disease stages and proliferation index value PI = 50%. Prognostic survival for these two patients is assessed correctly in the light of new research on the role of the tumor stroma for prognostics at triple negative breast cancer.

14. Conclusions

Survival at tumor recurrence in soft matter, after chemotherapy, is obtained in this paper.

This tumor recurrence is related to RNA folding at ion-jump concentration

and a temperature-quench. Therefore:

1) The folding state is considered as a cluster of aggregating proteins in cell division;

2) The conformation of the folding kinetics' two channels is accepted to be a knot "Figure-eight";

3) The folding is described as resonance of a relay relaxation oscillator, subjected to a periodic external influence of extending and folding forcing;

4) Diffusion at this resonance is determined as metastasis.

For tumor recurrence, in soft matter with the above RNA folding is designed a quantum model, with a minimal complexity:

1) Tumor memory is related to the maximal fidelity of this model;

2) Tumor recurrence oscillations are determined as probabilities' oscillations of this model;

3) Life stabilization marker is introduced, through considering the tumor recurrence oscillations as beneficial or detrimental for life.

From the designed quantum model with a minimal complexity are obtained:

1) Two types of tumor recurrence in soft matter-less widespread and dominant;

2) Chemotherapy intensity that acts as staggered magnetization.

Survival at tumor recurrence in soft matter, after chemotherapy, is determined by:

1) Type of tumor recurrence;

2) Life stabilization at tumor recurrence;

3) Interaction with the tumor microenvironment;

4) Chemotherapy intensity.

This survival is referred to one of the five regions of the ground-state phase diagram of "thermalizing", by the tumor microenvironment, a quantum model with a minimal complexity. To each of these regions is compared a survival class of a breast cancer patient.

It is presented that the survival at tumor recurrence in soft matter, after chemotherapy, provides a good idea of the actual survival of 32 patients with breast cancer.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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