Reorganization of actin filaments and microtubules by outside electric field

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REORGANIZATION OF ACTIN FILAMENTS AND MICROTIUBULES BY OUTSIDE ELECTRIC FIELD

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ABSTRACT

A theoretical study of the polymerization process of a cytoskeleton by an outside electric field is presented. We describe the reaction kinetics of polymerization of the cytoskeleton by Einstein's approximation. The thermodynamic study of the equilibrium constant of the reaction kinetics shows the possibility of the reorganization of the cytoskeleton by the outside electric field. We show an effective stimulation of the polymerization which is connected to the effective value of the electric field and can certainly be modulated by modulation of the carrier frequency.

Indexing terms/Keywords

Cytokolitodal polymerization, modulated electric field

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INTRODUCTION

The biophysical (biomechanical, bioelectrical, thermodynamic, etc.) properties of cells and their networks are studied intensively. This research is especially extended to understand the changes of these properties in various diseases. Cancerous cells attract huge attention from researchers, because the cellular changes and the network changes are obviously connected to one another. Twenty prestigious laboratories in the USA formed a research network (The Physical Sciences-Oncology Centers Network) to study these phenomena together. Their report about a complex study of malignant and benign tumour cell behaviour [1] is probably a milestone in this research. They observed definite and decisive differences between the mechanical, adhesion, and migration properties of the non-tumorigenic MDA-MB-231 and metastatic MDA-MB-231 U37 tumor cell lines, based mostly on multi-parametric approaches. The sharp mobility of cancer cells is probably connected to the lazy polymerization of the cytoskeleton [2], which promotes huge deformability in cancerous cases. The metastatic potential grows with increasing motility and high deformability [3]. Not only the cells but also the extracellular milieu have an important role in the metastatic mobility, showing a promoting role of the rigid extracellular matrix. However, the high motility is probably due to the loss of the polymerization order of the cytoskeleton [5], which makes the cells especially soft and movable [6].

Due to the importance of the appropriate polymerization of the cytoskeleton, we propose to enhance the polymerization with a modulated electromagnetic signal.

METHOD

The stoichiometric equation describing polymerization in reaction kinetics allows the following:

$$ M_1 + M_2 \rightarrow M_{11} $$

(1)

This kinetics could be formulated by the following reaction-kinetic equation:

$$ \frac{d[M_{11}]}{dt} = k_{+} [M_1][M_2] - k_{-} [M_{11}] $$

(7)

where \([\cdot]\) denotes the concentrations, and \(k_{+}\) and \(k_{-}\) are the speed constants of the forward and backward processes. In chemical equilibrium we have \(\frac{d[M_{11}]}{dt} = 0\), and consequently the equilibrium constant of the reaction:

$$ \frac{k_{+} [M_1][M_2]}{k_{-} [M_{11}]} = K $$

(3)

We study how the character of this reaction changes in an electromagnetic field and how it depends on the frequency and amplitude of the applied fields.

For a complete thermodynamic description, we consider three components of the system. Each component has its own polarizability interacting with the outside field. In this case the first law of thermodynamics is:

$$ dU = T dS - \mu P dV + \mu dN_1 + \mu_p dN_2 + \mu_d dN_3 + EdP_1 + EdP_2 + EdP_3 $$

(4)

where \(\mu_1, P_1\), and \(dN_1\) are the chemical potential, polarization, and particle number of the 1-range polymer \(M_1\); \(\mu_2, P_2\), and \(dN_2\) are the chemical potential, polarization, and particle number of the monomer \(M\); and \(\mu_3, P_3\), and \(dN_3\) are the chemical potential, polarization, and particle number of the range polymer \(M_{11}\). The difference is defined by the reaction during the time \(dt\) and \(F\) is the electric-field strength caused by the outside manipulation from independent sources. We consider the reaction at constant pressure and temperature (isobar and isothermal) and so we can introduce the free enthalpy as:

$$ dG = dU - T dS + pdV = \mu_1 dN_1 + \mu_2 dN_2 + \mu_3 dN_3 + EdP_1 + EdP_2 + EdP_3 $$

(5)

The condition of the polymerization equilibrium is when \(K = 0\) in (3). In this case we have an extreme problem with the definite stoichiometric condition described in (1). Introducing a reaction coordinate \(\xi\),
\[ dN_1 = -d \xi, \quad dN_2 = -d \xi, \quad dN_3 = d \xi \]  

(5)

Suppose that the polarization of the various components is proportional to the number of particles in the component:

\[ dP_1 = p_1 dN_1 = p_1 d \xi, \quad dP_2 = p_2 dN_2 = p_2 d \xi, \quad dP_3 = p_3 dN_3 = p_3 d \xi \]  

(7)

Then using (6), for equilibrium we obtain

\[ \frac{1}{T} \int \mu_0 + E p_1 + \mu_2 + p_2 E - \mu_3 - p_3 E \, d \xi = 0 \]  

(9)

When the actual time constants are smaller than the outside frequency, this equation is time-independent and so it is valid every time, so it has to be true for the average too:

\[ \frac{1}{T} \int \mu_0 + E p_1 + \mu_2 + p_2 E - \mu_3 - p_3 E \, dt = 0 \]  

(10)

The chemical potentials in the ideal-gas approximation are approached:

\[ \mu_1 = \mu_1^0 + kT \ln \langle M_1 \rangle, \quad \mu_2 = \mu_2^0 + kT \ln \langle M_2 \rangle, \quad \mu_3 = \mu_3^0 + kT \ln \langle M_3 \rangle \]  

(11)

where \( \mu_i^0 (i = 1, 2, 3) \) are the chemical potentials characterizing the unit concentration, and these can depend on the temperature. Substituting these into (9),

\[ \mu_0^0 + \mu_1^0 - \mu_3^0 + kT \ln \left( \frac{[M_1]}{[M_{11}]} \right) + \langle E p_1 + p_2 E - p_3 E \rangle = 0 \]  

(12)

where \( \langle \cdot \rangle \) means the time average. Consequently, the equation for reaction kinetics using the equilibrium constant from (3) is:

\[ K_n e^{-\frac{\mu_1^0 - \mu_2^0 + \mu_3^0}{RT}} = K_n e^{-\frac{\langle E p_1 + p_2 E - p_3 E \rangle}{RT}} \]  

RESULTS

The equilibrium constant when the electric field is zero is
\[ \frac{[M_f][M]}{[M_{f11}]} = \frac{k_v}{k_c} = K = e^{\frac{\mu_0^2 + \mu_1^2 - \mu_2^2}{kT}} = K_0(T) \]

Let us suppose that the polymerization effect of tubulins (which build the structure) at the temperatures \( k_v \) and \( k_c \) will decrease and increase with temperature, respectively. Consequently, from (13),

\[ \mu_0^2 + \mu_1^2 - \mu_2^2 > 0 \]

(14)

In consequence of (12), the effect of \( K(p_1 + p_2 - p_3) < 0 \) has the same process (growing length of tubulins), while in the case of \( K(p_1 + p_2 - p_3) > 0 \), the opposite occurs. When the polarization is proportional to the field, then:

\[ \frac{[M_f][M]}{[M_{f11}]} = \frac{k_v}{k_c} = K - e^{\frac{\mu_0^2 + \mu_1^2 - \mu_2^2}{kT}} e^{\frac{(\mu_0 + \mu_1 - \mu_2)^2}{kT}} = K_0 e^{\frac{\mu_0^2 + \mu_1^2 - \mu_2^2}{kT}} \]

(16)

When \( x_1 - x_2 = 0 \), then \( k_v \) decreases and \( k_c \) increases, so the field supports the polymerization. In the reverse case the outside field will dismount the cytoskeletal network.

The amplitude modulation has a special effect. The signal time-function of amplitude modulation of the carrier frequency \( \Omega_0 \) with angular-frequency \( \omega \) is

\[ u(t) - U_0 [1 + m \sin(\omega t + \phi)] \sin \Omega_0 t \]

(10)

where \( m \) is the modulation depth. The spectrum is shown in Figure 1.

**Figure 1. Spectrum of a carrier amplitude modulated by a harmonic frequency**

The effective potential is:

\[ u''_{eff} = \frac{U_0^2}{\gamma^2} + m^2 \frac{U_0^2}{4} \]

(17)

In consequence, the modulation increases the effective value of the electric field, and with this supports the reorganization of the cytoskeletal network according to (15). When the modulation is noise, then this effect is stronger, due to the non-discrete spectral frequency, but a continuous spectrum is applied.

Let us study an example with a modulated signal of:

\[ u(t) = x(t) U_0 \sin \Omega_0 t \]

(18)
where \( x(t) \) is pink noise (time fractal pattern).

When the power spectrum of the pink noise in the frequency interval \( [\omega_a, \omega_f] \) has the form of

\[
X(\omega)X^*(\omega) = \frac{A}{\omega}
\]

then the effective value of the modulated signal is

\[
u_{\text{eff}}^2 = \frac{\nu_0^2}{2} + 2A \ln \frac{\omega_f}{\omega_a}
\]

This shows that at \( \omega_a \to 0 \), \( \nu_{\text{eff}}^2 \to \infty \). Consequently, this type of modulation is excellent for reorganizing the cytoskeletal network.

**DISCUSSION**

The microtubules of the cytoskeletal network could be described by a polymer which Einstein proposed [7], [8]. It has a specialty that only a single chemical bond is allowed to be formed between the monomer and the prepared polymer. The reaction steps of this process are a chain polymerization (Einstein's polymer). This model is not able to describe the multi-bonding processes when the chemical bonds could have branches in the tubulins (multi-strands). When multi-bonding is allowed, the reaction can have active inside a strand of polymer chain, making various space-filling structures.

The polymerization steps of linear polymers can be described by equilibrium constants:

\[
K_1 = \left[ \frac{[M]}{[M]_1} \right], K_2 = \left[ \frac{[M]_2}{[M]} \right], ..., K = \left[ \frac{[M]_n}{[M]} \right]
\]

The polymerization steps in Fig. 3 need the following equilibrium constants:

\[
K_1 = \left[ \frac{[M]}{[M]_1} \right], K_1' = \left[ \frac{[M]_1}{[M]} \right], K_2 = \left[ \frac{[M]_2}{[M]_1} \right], ..., K = \left[ \frac{[M]_n}{[M]_{n-1}} \right], K = \left[ \frac{[M]_n}{[M]_{n+1}} \right]
\]

These equilibrium constants can differ. The reorganization stimuli are valid for these multi-strand cases too, but the multi-strands have longer chains than the monomer strand does. This is because the multi-strand polymer has multiple free ends and energy changes, so these are less favorable from an energy point of view. According to the Boltzmann statistical considerations a system with multi-strand chains will have a lower concentration than one with mono-chains. On the other hand, there is a connection between the concentration of polymer \( [M]_n \) and its length expressed in the number of monomers from which it is constructed, expressed as

\[
[M]_n \propto c_n^{-n/2}
\]

where \( n \) is constant. Consequently, the low concentration has longer polymers.

**CONCLUSION**

We have shown the possibility of polymerization support of the cytoskeleton. This idea is especially important in the case of cancer cells, where the destabilized and incompletely polymerized cytoskeleton has the role of allowing higher motility of these cells, promoting the metastatic spread. Our method is applied well in practice, where we use fractal noise for proper action [9]. Our approach using noise is similar to the harmonizing method [10], whose application is emerging in physiology [11].

**REFERENCES**


Author's biography with Photo

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PERSONAL

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1967-72 Studio of Eötvös University (Physics) (MS graduation, thesis: Polaron annihilation)

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