A CONCISE REVIEW OF SOFT GLASSY RHEOLOGICAL MODEL OF CYTOSKELETON

Yogesh Deepak Bansod, Jiří Burša*

A cytoskeletal network contributes significantly to intracellular regulation of mechanical stresses, cell motility and cellular mechanics. Thus, it plays a vital role in defining the mechanical behaviour of the cell. Among the wide range of models proposed for dynamic behaviour of cytoskeleton, the soft glassy rheology model has gained special attention due to the resemblance of its predictions with the mechanical data measured from experiments. The soft glassy material, theory of soft glassy rheology and experiment on cytoskeleton has been discussed, which leads to a discussion of the unique features and flaws of the model. The soft glassy rheological model provides a unique explanation of the cytoskeleton ability to deform, flow and remodel.

Keywords: *cytoskeleton, model, sglassy rheology, magnetic twisting cytometry*

1. Introduction

The cytoskeleton (CSK) is an interconnected structure of various cross-linked and interlinked filamentous biopolymers that extends from the nucleus to the cell surface. The mechanical forces of the cytoskeleton are associated with many biological functions of cells such as its growth, differentiation, and apoptosis, (programmed cell death) which cause the changes in cell shape [1]. Numerous evidences have shown that CSK plays a vital role in transmitting mechanical stresses from the cell surface to the nucleus across the cytoplasm [2, 3, 4, 5].

The cytoskeletal network is composed of three types of filaments: actin filaments, microtubules and intermediate filaments [6] as shown in Fig. 1. The actin filaments (diameter of 6–8 nm) are woven into network with little extensible cross-linked filaments [7]. These filaments are in tension due to the cell contractile apparatus and also passively by the cell distension through its adhesive substrate or by the swelling pressure of liquid cytoplasm [2]. Microtubules are tubular biopolymers (outer and inner diameter of 24 and 12 nm, respectively) [7] and are in compression to resist the contraction from interconnected actin network [8]. Intermediate filaments (diameter of 10 nm) that are believed to be in tension contribute significantly to cell stiffness only at large strains ($> 20\,\%$) [9]. These three filamentous networks are physically interlinked [10] which enable a force transmission among them.

During their spreading process, most of the cells are anchored to the extracellular matrix (ECM) to balance the forces induced by the CSK filaments to achieve equilibrium. The transmembrane integrin receptors concentrated in focal adhesion plaques transfer a portion of the mechanical forces within the CSK to the ECM [11]; as a consequence traction forces rise at the cell-ECM interface. These traction forces are in equilibrium with forces within

* Y. D. Bansod, M.Sc., prof. Ing. J. Burša, Ph.D., Institute of Solid Mechanics, Mechatronics and Biomechanics, Faculty of Mechanical Engineering, Technická 2896/2, 616 69 Brno, Czech Republic

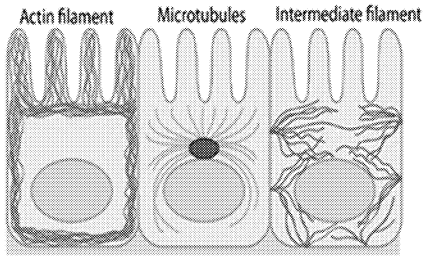

Fig.1: (a) actin filaments are mainly concentrated on the cell cortex; (b) microtubules are developed from the centrosome near the nucleus; (c) intermediate filaments are distributed in the central regions of the cell and across to neighbouring cells

the CSK [2]. Thus, understanding of CSK stabilization leads to recognition how living cells can sense and respond to the mechanical stresses. The mechanical models of living cells have been generally described either by microstructural or continuum approaches [12, 13].

A soft glassy rheological model is based on the measurement of cell mechanics. Cytoskeletal mechanics plays a vital role in the cellular mechanotransduction and motility that involves in contraction, spreading, and crawling. It also plays a key role in other mechanical functions such as cell division and apoptosis. In this context, rheological properties of the cytoskeleton are of uttermost importance [14].

2. Experiments on cytoskeleton

2.1. Soft glassy material (SGM)

Soft glassy materials comprise a diverse group of substances that include foams, pastes, colloids, emulsions and slurries [14, 15, 16]. The empirical criteria that define this class of materials are as follows: they are very soft, both elastic modulus, $G'(\omega)$ and loss modulus, $G''(\omega)$ increase with the same weak power-law dependencies upon frequency, hysteresivity, η (ratio of loss to elastic modulus) is frequency insensitive and of the order 0.1 and under certain conditions they display physical aging behaviour [15, 17, 18]. At a given frequency, both $G'(\omega)$ and $G''(\omega)$ moduli increase linearly with an increasing prestress [19]. The generic feature shared by all soft glassy materials is each one of them is composed of elements that are discrete, numerous, and aggregate with one another via weak interactions [18].

2.2. Magnetic Twisting Cytometry (MTC)

Considering a parallelism between the living cells and SGM, it was hypothesized in [14] that the CSK can be added to the list of SGM and may be modelled using a soft glassy rheology theory (SGR) proposed by Sollich [17]. Magnetic twisting cytometry (MTC) has been performed to obtain the mechanical response of variety of cells; in this method the cell is sheared between a plate at the cell base and a magnetic microsphere partially embedded into the cell surface, as shown in Fig. 2(a) and (b). The magnetic twisting field introduces a torque and thus causes the bead to rotate and displace as shown in Fig. 2(c), which is detected by a CCD camera mounted on an inverted microscope.

The frequency dependence of both G' and G'' has been then extracted from the structural response at the point of bead attachment [14]. Results are shown in Fig. 3, G' increases with increasing frequency, ω according to power law $\sim \omega^{x-1}$ with effective temperature or

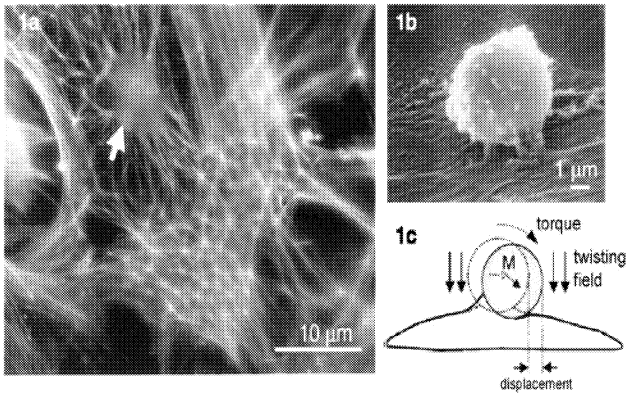

Fig.2: (a) and (b) beads attached to the cytoskeleton of human airway smooth muscle (HASM) cells via cell adhesion molecules (integrins); (c) the application of magnetic field and the displacement of the bead [16]

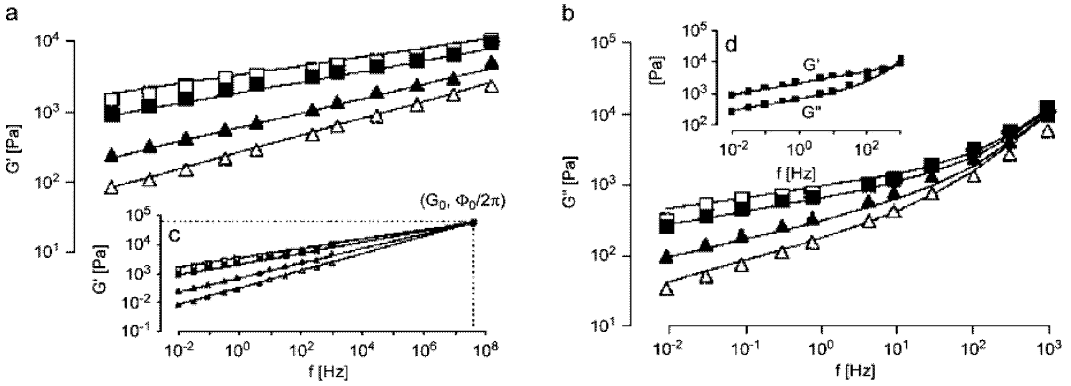

Fig.3: (a) and (b) represent the elastic modulus, $G'(\omega)$ and loss modulus, $G''(\omega)$ as functions of frequency, ω for different drug treatments; filled squares represent response under control conditions, unfilled squares are for treatment with histamine, filled triangles depict treatment with DBcAMP and unfilled triangles indicate treatment with cytochalasin D. The solid lines satisfy the structural damping equation with the values of scale factor for stiffness, $G_0 = 53.6\,kPa$ and frequency, $\Phi_0 = 25{\times}10^7\,rad/sec$, and viscosity constant $\mu = 1.41\,Pa\,s$. (c) Extrapolation of Eq. (2) to higher frequencies yields crossover at coordinate (G_0, Φ_0). (d) Dynamic moduli under control conditions [16]

noise level, x equals to 1.20 under control conditions. Similarly, G'' also increases with increasing frequency and follows the same power law in the range of $0.01-10\,\mathrm{Hz}$ [14, 16]. On the contrary, within the same frequency range the loss tangent was relatively frequency insensitive [15].

2.3. The structural damping equation

In time domain, the mechanical stress response $G(t)$ to a unit step change in strain imposed at $t = 0$ is given by

$$G(t) = \mu\,\delta(t) + G_0 \left(\frac{t}{t_0}\right)^{(1-x)} . \tag{1}$$

Here, G_0 is the ratio of stress to the unit strain measured at an arbitrary chosen time t_0, μ is a Newtonean viscous term and $\delta(t)$ is the Dirac delta function. The complex modulus for the same can be given as

$$G(\omega) = G_0 \left(\frac{\omega}{\Phi_0}\right)^{(1-x)} (1 - \mathrm{i}\,\eta)\,\Gamma(2-x)\,\cos\frac{\pi}{2}(t-1) + \mathrm{i}\,\omega\,\mu \tag{2}$$

where, η is called as structural damping coefficient, ω is the radian frequency $2\,\pi\,f$, G_0 and Φ_0 are scale factors for stiffness and frequency, respectively, Γ denotes the Gamma function and $\mathrm{i}^2 = -1$, G_0 and μ depend on bead-cell geometry.

In the above equation, the elastic modulus, $G'(\omega)$ corresponds to the real part which increases for all values of ω according to the power law exponent, $x - 1$ [14]. On the other hand, the loss modulus $G''(\omega)$ corresponds to an imaginary part and is a frequency-independent fraction η of the elastic modulus; such a direct coupling of the loss modulus to the elastic modulus is the characteristic feature of structural damping behaviour [20]. Loss modulus also includes a Newtonean viscous term, $\mathrm{i}\,\omega\,\mu$ which comes into play only at higher frequencies. The key characteristic of glassy materials is that, they are not in thermodynamics equilibrium below their glass transition temperature, T_g. In addition, these materials are arrayed in a microstructural geometry that is structurally disordered and metastable [14]. The structural damping coefficient η is not an independent parameter but depends on x only [15].

3. Soft glassy rheology (SGR)

3.1. Theory of soft glassy rheology

Sollich [18] extended the earlier work of Bouchaud's glass model [21] to develop the unified theory of SGR. This theory considers that each individual element of the matrix exists within an energy landscape containing many wells of differing depth. These traps are formed by interactions of an element with neighbouring ones. Each of the energy well is regarded as being so deep that the elements are unlikely to escape the well by thermal fluctuations alone. Instead, elements are imagined to be agitated and rearranged by mutual interactions with neighbouring elements within the matrix. This agitation can be represented by an effective temperature or noise level, x [17, 18].

In Eq. (2) when $x > 1$, there is sufficient agitation in the matrix for an element to hop randomly between the wells. Consequently, the system becomes disordered and as a whole

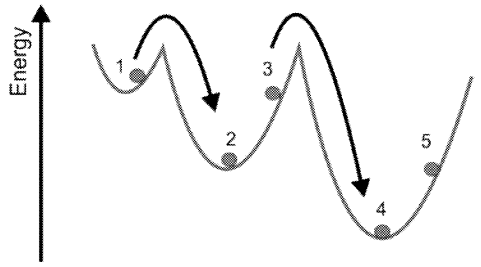

Fig.4: Schematic illustration of the soft glassy rheology model of the cytoskeleton in which the natural reorganization and dynamics for intracellular biopolymers can be modelled as a series of transitions (positions 1–5) between a fluid and solid state [22]

it can flow. It thus behaves like a glassy material. However, when x approaches 1, the element is trapped in such a deep well that the agitation in the matrix (under a given temperature and noise level) is not high enough to hop off. Consequently, the system becomes stabilized and thus behaves like an elastic material. The higher the effective temperature, x the more frequently an element trapped in the energy well manages to hop from this well into another [17]. Thus the hop can be viewed as the fundamental molecular remodelling event [23].

3.2. Sollich's evolutional probability equation

The SGR theory follows a conservation law for probability $P(E,l,t)$ of an element being trapped in an energy well of depth E and local displacement l, at time t:

$$\frac{\partial P(E,l,t)}{\partial t} - \gamma \frac{\partial P}{\partial l} = -g(E,l)\, P(E,l,t) + f(E)\, \varphi(t)\, \delta(l) \ . \tag{3}$$

Where, $\varphi(t) = \int \mathrm{d}E\, \mathrm{d}l\, g(E,l)\, P(E,l,t)$ (required for conservation of probability), $\delta(l)$ is the Dirac delta function and $f(E)$ is the distribution of energy well depths. The above equation is known as structural or hysteretic damping; the second term on the left hand side represents the change in probability because of the motion of the energy trap itself, E, while the first term on the right hand side is depletion, equal to the probability of resident elements to be hopping out, given by the product of the probability of occupancy P and a transition rate $g(E,l)$. The second term on the same side is an accumulation rate, equal to the product of the total number of available transitions $\varphi(t)$ and the delta function constraint forcing elements to hop into the wells at zero local strain. The $\delta(l)$ function is due to the assumption that the local strain becomes zero immediately after the relaxation [16, 17, 23].

Sollich has taken

$$f(E) = \exp(-E) \qquad \text{and} \qquad g(E,l) = \Phi_0 \exp\left(-\frac{E + \frac{k\, l^2}{2}}{x}\right) \ .$$

The transition $g(E,l)$ rate for hopping out of wells is distributed over E, which is a nonlinear regime and function of strain. It must be noted that the selection of energy well is not correlated with the previous position [15]. In structural damping Eq. (2), when $x > 1$, there is sufficient agitation in the matrix that the element can hop randomly between wells as a result, the system as a whole can flow and become disordered which are the fundamental features of glassy materials [17].

4. Discussion

Fabry et al. [14] used the magnetic twisting cytommetry with optical detection of bead motion for measurement of human airway smooth muscle cell and suggested that the CSK proteins might regulate cell mechanical properties mainly by modulating the effective noise temperature, x of the cytoskeletal network. In other words, the effective noise temperature, x measures the CSK ability to deform, flow and reorganize. Further, the weak power-low dependence of both elastic and frictional moduli on the frequency over a wide frequency range characterized the dynamic behaviour of adherent cells. The cells as a soft glassy material lie close to the glass transition [14, 15, 16]. It has been noted that the prestress of CSK and

effective noise temperature have a unique inverse relationship [24]. Both dynamic elastic moduli and frictional moduli increase linearly with the increasing CSK prestress [19]. The unique features of soft glassy rheology theory make it well-suited to describe the rheological behaviour of cytoskeleton.

However, nothing has been mentioned about the regulation of effective temperature or noise level in the cells (either by drugs or mechanical stimuli, etc.) An unidentified but non-thermal origin has been used by Sollich as a jostling of elements to interpret the effective noise temperature, x. The parameters that determine the scale factor for frequency, Φ_0 in the Sollich's evolution equation are yet unexplained. There are difficulties with the interpretation of depth of the energy well, E [14]. Prestress, which plays a significant role in defining the steady-state behaviour of the cell, is not taken into consideration by soft glassy rheology theory [6].

5. Conclusion

This review showed that the soft glassy behaviour and the underlying notion of the noise temperature might provide a unique explanation of the cytoskeleton ability to deform, flow and remodel. It can also be stated that the structural disorder and metastability are the essential features that may comprise the basis of cytoskeleton mechanical functions.

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