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Continuum-Based Modelling Approaches for Cell Mechanics

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***Abstract*—**The quantitative study of cell mechanics is of paramount interest, since it regulates the behaviour of the living cells in response to the myriad of extracellular and intracellular mechanical stimuli. The novel experimental techniques together with robust computational approaches have given rise to new theories and models, which describe cell mechanics as combination of biomechanical and biochemical processes. This review paper encapsulates the existing continuum-based computational approaches that have been developed for interpreting the mechanical responses of living cells under different loading and boundary conditions. The salient features and drawbacks of each model are discussed from both structural and biological points of view. This discussion can contribute to the development of even more precise and realistic computational models of cell mechanics based on continuum approaches or on their combination with microstructural approaches, which in turn may provide a better understanding of mechanotransduction in living cells.

***Keywords*—**Cell mechanics, computational models, continuum approach, mechanical models.

I. Introduction

LIVING cells in human body are continuously subjected to the myriad of extracellular and intracellular mechanical stimuli and in response they generate stresses and strains. It has been observed in different experiments, that the cell deformation can affect both their physiological functions as well as biological processes. The novel experimental techniques provide substantial information regarding the mechanical properties of the cell along with their responses to diverse chemical and mechanical stimuli. This leads to the development of new theories and mechanical models of living cells that can characterize cell responses when subjected to distinct loading types.

There are innumerable computational models at distinct temporal and spatial scales that have been developed to capture and simulate the cell responses corresponding to the experimental observations. The existing computational modelling approaches for cell mechanics are broadly classified into two categories namely the continuum approaches and the microstructural approaches, which are outlined in Fig. 1 [30]. The microstructural approaches consider the cytoskeleton (CSK) as the critical component in cell mechanics. Whereas the continuum approaches ignore the contribution of distinct molecular structures to cell mechanics and are employed when the smallest length scale of interest is much larger than the space over which the structures and properties of the cell vary significantly [30].

The continuum mechanics uses coarse-graining approach to localize the microscopic stress-strain relationships, which then yields a constitutive relationship and deformation description of the material that can be applied at macroscopic scale. The models under continuum paradigm are validated and the associated material constants are evaluated by comparing the results obtained from canonical experimental techniques with computational predictions [31]. The finite element method is the frequently used technique in computational simulations to study a variety of cellular processes, whereas the boundary element method has also been employed as an alternative technique wherever necessary [31].

The majority of the mechanical models under continuum paradigm assume that cell is passive in nature. Recent studies have successfully overcome this drawback by incorporating the inherent active nature of the cell in computational modelling [6]. This review article outlines the existing mechanical models of cell mechanics that are premised on the continuum mechanics**.**

II. Liquid Drop Models

The suspended cell types (like neutrophils, leukocytes, and erythrocytes) often adopt spherical shape and behave like a liquid droplet. In micropipette aspiration at certain threshold of pressure difference, these cells can be aspirated into a micropipette with a smaller diameter and then, upon release they regain their initial spherical shape. The liquid drop models also known as cortical shell-liquid core models were invented to elucidate this rheological behaviour of suspended cells. These models view the suspended cell or its parts as a deformable material with certain continuous material properties. This class of models incorporates the Newtonian liquid drop model, the compound Newtonian liquid drop model, the shear-thinning liquid drop model, and the Maxwell liquid drop model [1].

A. Newtonian Liquid Drop Model

The Newtonian liquid drop model has been invented to simulate the continuous deformation of leukocytes when flowing into the micropipette [1]. The cell is modelled as Newtonian liquid droplet as depicted in Fig. 2 (a).

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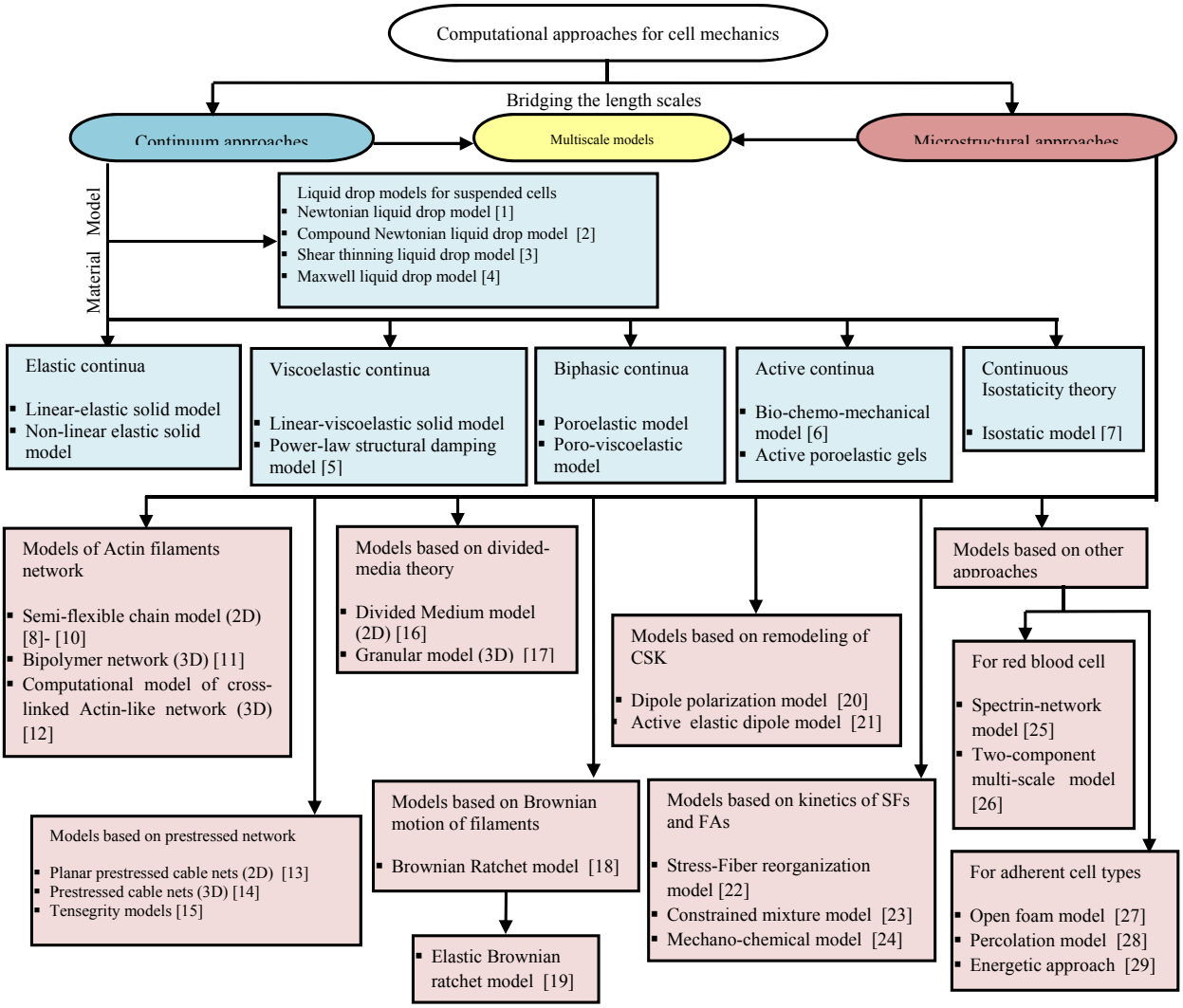

Fig. 1 The schematic representation of computational approaches (continuum and microstructural) for cell mechanics (modified from [30])

The outer cortex was assumed viscous fluid with constant surface tension and no bending resistance circumscribing its endogenous part, which was assumed homogenous Newtonian viscous liquid [1]. The state of stress is considered independent of any displacement and the constitutive relations for the cortex are described by two equilibrium equations as

$$(T_1 + T_2)/2 = T_0 + k(V_a/2), \quad (T_1 - T_2)/2 = \eta V_s, \quad k = 3\eta \tag{1}$$

where T_1 and T_2 are the in plane principal stress resultants, T_0 is the static in-plane isotropic tension corresponding to zero shearing and dilatory rates, k and η are the coefficients of viscosity for surface area dilation and shear respectively, and V_a and V_s are the rates of dilation and shear, respectively [31].

The micropipette aspiration of neutrophil indicates that the cytoplasm behaves as a Newtonian fluid. The relationship between the rate of the change of the projection length of the cell inside the pipette $\dot{L}$ and the radius of the cell outside the pipette R_c [32] is described as

$$\frac{(\Delta P - P_{cr})}{\mu\,(\dot{L}/R_P)} = m\left(1 - \frac{R_P}{R_c}\right) \quad \text{for } 0.5 \le \mathrm{R_P/R_c} \le 1.0 \tag{2}$$

where

$$P_{cr} = 2T_0\,(1/R_P - 1/R_c) \tag{3}$$

where ΔP is the total suction pressure, P_{cr} is the critical excess suction pressure, μ is the shear viscosity, R_P is the radius of the pipette, and m is a coefficient that is dependent on the ratio of the cortical dissipation to the core dissipation $\tilde{\eta}$. Here, $m \approx 6$ corresponds to $\tilde{\eta} \approx 0.01$[33].

This model was devised to study the recovery behaviour of neutrophil after going through large deformation in micropipette aspiration test. The theoretical recovery process was obtained as a function of non-dimensional time and the initial deformation ratio. Some of the experimental observations of this model are in accordance with the theoretical predictions indicating that the Newtonian liquid

drop model can predict the overall deformation of the cell and its ability to recover its original shape [34]. However, it neither illustrates the initial rapid entry of the cell into the pipette [31], [32], [34], [35] nor its resistance to mechanical stresses [30]. Apart from this, due to several discrepancies between this model's predictions and experimental findings [3], [33], [34], [36], this leads to the development of the compound Newtonian liquid drop model [3].

B. Compound Newtonian Liquid Drop Model

It has been observed that in different experiments that nucleus is stiffer and more viscous than its circumscribing cytoplasm [2], [37]-[39]. The compound Newtonian liquid drop model, which is a refinement of the earlier model, views cell as a heterogeneous structure composed of three layers as illustrated in Fig. 2 (b) [2]. The outer layer describing the plasma membrane is modelled as a thin cortical shell with constant isotropic surface tension. The middle thick layer representing the cytoplasm is modelled as the Newtonian fluid with relatively small viscosity. The inner layer characterizing the segmented nucleus surrounded by CSK is also modelled as Newtonian liquid, but with relatively large viscosity [35]. This layer is under constant cortical tension due to nuclear envelope [40].

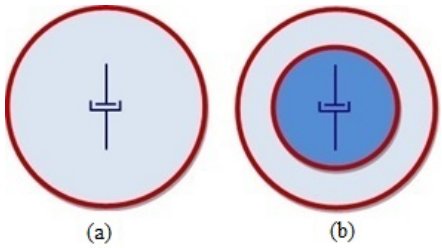

Fig. 2 (a) The Newtonian liquid drop model: An intracellular region is modelled as Newtonian liquid (light blue) surrounded by cortex (red) modelled as fluid layer with constant tension. (b) The Compound Newtonian liquid drop model: An intracellular region is comprised of heterogeneous parts where the nucleus is modelled with more viscous Newtonian fluid (dark blue) than the circumscribing cytoplasm (light blue) and is enclosed by the nucleus cortex layer of static surface tension (red). The plasma membrane is modelled as pre-stressed cortical shell (red) (modified from [31])

This model predicts a smaller viscosity in larger pipet for small deformation analysis [35]. Further, it can exhibit Newtonian behaviour [34] by tuning the time scale ratios of the nucleus and the cytoplasm [41], [42]. This model can grasp the initial fast recoil phase of the recovery process, which indicates that it can describe the non-Newtonian behaviour of the cells as well [41], [42]. It has been evident that the nucleus plays a vital role in defining the leukocyte rheological behaviour, which depends on the ratio of the surface tension, the ratio of the viscosity between layers, and the extent of deformation of the nucleus [40], [41]. The set of mechanical parameters of this model cannot be deduced by recovery experiment alone [31].

C. Shear Thinning Liquid Drop Model

The study of non-Newtonian behaviour of the cell served as a motivation to develop the Shear thinning liquid drop model. As demonstrated in Fig. 3 (a), the cytoplasm is modelled as a homogenous non-Newtonian fluid bounded by a layer with constant surface tension representing the cortex of the cell. It evaluates the changes in apparent cytoplasmic viscosity of the cell corresponding to an applied shear rate at a large deformation [3].

It has been observed in the experiments that increase in the mean shear rate causes decrease in the apparent cytoplasmic viscosity η conforming to power-law relationship as follows

$$\eta = \eta_c \, (\dot{\gamma}_m/\dot{\gamma}_c)^{-b} \tag{4}$$

Here η_c is the characteristic viscosity at characteristic shear rate $\dot{\gamma}_c$, b is the power, and $\dot{\gamma}_m$ is the mean shear rate averaged over the whole process and domain [3], [31]. The constitutive relationship for the Newtonian liquid drop model at constant shear rate $\dot{\gamma}$ gives

$$\tau = \eta_c \, (\dot{\gamma}_m)^{-b} \dot{\gamma} \tag{5}$$

The Shear thinning liquid drop model can explain well the non-linear deformation of the cell at its entrance into the micropipette compared to the Newtonian liquid drop model. The finite element analysis of the model not only elucidates the basic relationship between the aspiration rate and the micropipette diameter, [43] but also demonstrates the ejection behaviour of the cell [44]. Nonetheless, this model is not able to forecast the initial phase of rapid entry of the cell into the micropipette [3]. In addition, a number of cell types did not reveal the shear-thinning behaviour when subjected to small strain deformations [45].

D. Maxwell Liquid Drop Model

The Maxwell's liquid drop model has been proposed to explicate the rapid initial entry of the cell into the micropipette at the beginning of the aspiration test. It premises the cell as pre-stressed static-tension cortical shell containing incompressible Maxwell viscoelastic fluid [4] as depicted in Fig. 3 (b). This model encompasses an elastic element, which makes it different from the Newtonian liquid drop model [1]. The constitutive relationship is given by

$$\tau + \frac{\mu}{k} \dot{\tau} = \mu \dot{\gamma} \tag{6}$$

where τ is the shear stress, μ is a viscous constant of a dashpot arranged in series, k is an elastic constant of a spring, $\dot{\tau}$ is the shear stress rate, and $\dot{\gamma}$ is the shear strain rate [4], [31].

For a small strain aspiration test, results obtained using series solutions and the finite element method demonstrated that this model could interpret the initial rapid entry and the recovery behaviour of the cell [4]. It has been observed, that in the initial phase of the micropipette aspiration test when the deformation is rapid but small, the cytoplasm behaves like the Maxwell fluid for a very short duration, whereas in later phase when the deformation is large but slow, it behaves more like

the Newtonian fluid of high viscosity [46]. In the large deformation finite element simulations of aspiration test, the model was not able to produce valid results unless both the viscous and elastic coefficients of the Maxwell fluid were increased steadily as the cell was sucked into the micropipette. This infers that the Maxwell liquid drop model is not able to explain the rheological properties of the cell [2], [46], [47].

All liquid drop models analysed under similar boundary conditions may exhibit a linear dependence of stiffness on pre-stress [48]. Even though the results provided by liquid drop models are in accordance with the experimental findings under specific experimental conditions, in general they are not able to predict (from the mechanistic principles) how these properties can influence the cell functions. In addition, they are also not able to predict the resistance of living cells to mechanical stress [30].

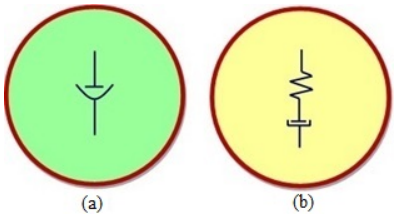

Fig. 3 (a) The shear thinning liquid drop model: An intracellular region is modelled as a homogenous non-Newtonian fluid (green). (b) The Maxwell liquid drop model: An intracellular region is modelled as a homogenous Maxwell fluid (yellow). In both models, an intracellular region is surrounded by pre-stressed cortical shell (red) (modified from [31])

III. Elastic Continua

The elastic or viscoelastic solid models were invented to capture the solid-like behaviour of the cell into micropipette aspiration. They consider the cell as an elastic or viscoelastic incompressible and homogenous half-space [49]-[51]. This class of models are different from the preceding ones in the sense that the cell is considered either as homogenous or heterogeneous solid (nucleus is defined discretely embedded in the cytoplasm) without accommodating the distinct cortical layer [31]. The material models belonging to this class are the linear elastic models, non-linear elastic models (hyper-elastic), and linear-viscoelastic models.

A. Linear and Non-Linear Elastic Solid Models

In both linear and non-linear elastic (hyper-elastic) solid models, the cell is represented as homogenous solid and the time factor is disregarded [31]. The elastic behaviour of the linear model follows the Hooke's law, whereas the non-linear model does not [44], [52]. Both, the linear and non-linear elastic model could be useful for finding the material properties of the cell subjected to small and large deformations, respectively. The linear elastic solid model coupled with the tensegrity model is simulated to determine the mechanical behaviour of the smooth muscle cell subjected to compression and indentation test [53]. As these models are highly oversimplified compared to the intricate living cells they are not able to explain some of the natural cellular characteristics such as motility [54].

IV. Viscoelastic Continua

A. Linear Viscoelastic Solid Models

The linear viscoelastic solid models have been proposed to study both solid and fluid like material properties of the cell.

In this approach, the cell is illustrated as either homogenous or heterogeneous solid where the stress is linearly dependent on strains and their time derivatives [44], [55]. These models are deduced to unravel the obscure behaviour of cell under transient loading conditions, that is creep or stress relaxation. They are able to characterize the nucleus and the cytoplasm separately [56], [57]. In conjunction with other models, these models are employed to investigate the changes in cell mechanics during cell migration [58] and deformation [51]. Recently, a finite element viscoelastic model has been developed to forecast the osteoblast behaviour subjected to cyclic isotropic radial strain [59].

In the computational simulation of single cell experiments to evaluate the cell deformation the neo-Hookean hyper-elastic [56], [57] and the standard linear solid (Klevin) models are the widely used non-linear elastic and linear viscoelastic type of solid models, respectively [31], [60].

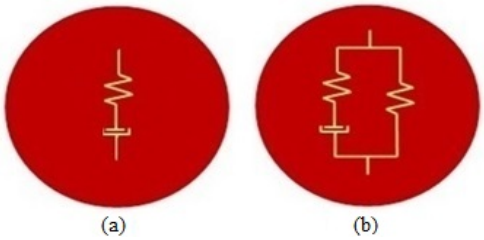

Fig. 4 The whole cell is modelled as (a) linear elastic solid and (b) linear viscoelsatic solid (modified from [31])

Both the linear elastic solid model depicted in Fig. 4 (a) and the linear viscoelastic solid model depicted in Fig. 4 (b), were developed to mimic different observations of the single cell experiments. They have been enormously used in computational simulations of distinct cell types undergoing different mechanical tests and are summarized in TABLE I. The major drawback of both solid models is that a unique set of material properties cannot be employed to simulate the mechanical behaviour of both the suspended and adherent cell types [44].

B. The Power-Law Structural Damping Model

In the last decade, the power-law structural damping model also known as Soft Glassy Rheological (SGR) model has gained great acclaim in the field of cell biology due to its unique ability to predict the power-law as well as other time-dependent types of behaviour observed in living cells. A phenomenological model based on SGR theory has been proposed to evaluate the dynamic behaviours of cells subjected to the time-varying forces. This model describes the

cell as soft glassy material existing close to the glass transition, and suggests that the CSK proteins may govern the mechanical properties of cells mainly by modulating the effective noise temperature of the matrix [5].

The class of soft glassy materials comprises of a diverse group of substances that include foams, pastes, colloids, emulsions, slurries etc. The materials under this paradigm are composed of elements that are discrete, numerous, and aggregated with one another via weak interactions. In addition, they are not in thermodynamic equilibrium below glass transition (similar to glass thus, sometimes called as soft-glassy materials) and their geometrical arrangement is structurally disordered and metastable [75].

TABLE I
THE SOLID MODELS WERE DEVELOPED ON THE BASIS OF OBSERVATIONS OF THE CORRESPONDING EXPERIMENTAL METHODS AND THEIR IMPLEMENTATION IN THE COMPUTATIONAL SIMULATION TO EVALUATE THE DEFORMATION OF VARIOUS CELL TYPES

Material Model	Experimental Method	Cell Types
Linear and non-linear elastic	Micropipette aspiration [49] Atomic force microscopy [61] Cytointender [62] Magnetic twisting cytometry [63]	Stem cells [65], [66] Osteosarcoma cells [67], Vascular endothelial cells [68], Bovine endothelial cells [69], [70], Endothelial cells and their nuclei [38], [49].
Linear viscoelastic	Micropipette aspiration [50] Flat punch indentation[64]	Myoblasts [57], Chondrocytes and their nuclei [37], [71] Endothelial cells [72], Leukocytes [73], Osteocytes [74].

The SGR theory considers that each individual element of the cytoskeletal matrix exists within an energy landscape containing many wells of varying depths as depicted in Fig. 5.

In case of living cells, these wells are thought to be formed due to the binding energies between the neighbouring cytoskeletal elements. Due to lack of thermal energy in the system, it is not able to undergo structural rearrangement, and because of this, the elements are unlikely to escape from the energy wells [76]. Over the time, the element escapes from the energy barriers of neighbouring elements and hops out of that well to fall into another, reaching a more stable state with very slow relaxation rates [77]. In such systems, the non-thermal energy source provides agitation (represented by an effective temperatures, or noise level, *x*) to the elements so that they can hop out from the energy well in which they are trapped. Because of this, the system undergoes structural rearrangement causing the material to flow [76].

The structural damping model that follows the power-law trend has been proposed in [5] to describe the frequency-dependent rheological behaviour of adherent cell types. The complex modulus $G^*(\omega)$ of this model is expressed as

$$G^*(\omega) = G'(\omega) + iG''(\omega) = G_0\left(\frac{\omega}{\Phi_0}\right)^{x-1}(1+i\bar{\eta})\Gamma(2-x)\cos\frac{\pi}{2}(x-1) + i\omega\mu \quad (7)$$

where *x-1* is the power-law exponent, $\bar{\eta}$ is the structural damping coefficient given by $\bar{\eta} = G''(\omega)/G'(\omega) = \tan\left((x-1)\pi/2\right)$, ω is the radian frequency $2\pi f$, G_0 and Φ_0 are scaling factors for the stiffness and frequency, respectively, Γ denotes the Gamma function, $i^2 = -1$, and both G_0 and μ (viscosity material parameter [Pa.s]) depend on bead-cell geometry [55]. The elastic modulus also known as storage modulus $G'(\omega)$ corresponds to the real part of (7), which increases for all values of ω according to the power-law exponent, whereas the loss modulus $G''(\omega)$ corresponds to an imaginary part of (7), and includes a component that also increases as a power-law with same exponent. The loss modulus is a frequency-independent fraction $\bar{\eta}$ of the elastic modulus; such direct coupling of the loss modulus to the elastic modulus is a characteristic feature of structural damping behaviour. The loss modulus also includes a Newtonian viscous term $i\omega\mu$, which comes into play only at higher frequencies. The changes in exponent of the power-law (7) describes the transition from solid state ($x=1$) to liquid state ($x=2$) [5].

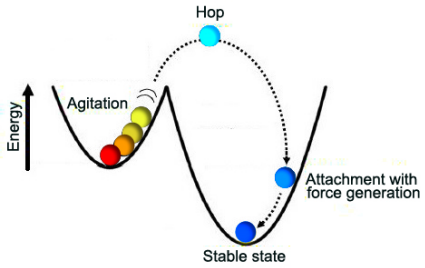

Fig. 5 The schematic illustration of trap dynamics in SGR model of CSK, the natural reorganization and dynamics of intracellular biopolymers can be modeled as an array of transitions between a fluid and solid state. This is illustrated by hopping of elements between the energy wells of varying depths, reaching a more stable state [78]

It has been experimentally observed that under controlled conditions the dynamic moduli increases with increasing frequency following the weak power-law [45]. The frequency-dependent response of a single cell can be given by two regions of diverse rheology; at actin cortex, the power-law is lower and the region is more elastic, on the contrary, an intracellular region has a higher power and is more liquid-like [79]. The pre-stress that regulates the transition between the solid-like and fluid-like behaviour in cells has a unique inverse relationship with the power-law exponent. The dynamic moduli ($G'$and G'') increase linearly with increase in the cytoskeletal pre-stress [59].

It has been evident in various experiments, that the cells can demonstrate some of the key characteristics of soft glassy materials like dynamical heterogeneity, physical aging, and shear-induced rejuvenation, which are in favour with SGR model [45], [52], [79]. A material law related to Power-Law Rheology (PLR) model has been developed and incorporated in the biomechanical model of the cell in micro bead twisting experiments, which deduces the material constants related to PLR using the finite element method [80], [81]. Recently, a similar model has been developed and implemented in

computational simulation of cell in micropipette aspiration [82].

This model has an advantage over the solid viscoelastic models due to its ability to manifest dynamic behaviour of the cells following power-law trend [31]. It has been employed to simulate the dynamic response of a cell in various experimental techniques for instance magnetic twisting cytometry [45], [80], [81], atomic force microscopy [83], and micropipette aspiration [82]. Nevertheless, an unidentified non-thermal origin of the effective temperature has been used in this model and there are difficulties in interpreting the depth of the energy wells [84]. As assumed by this model the biological responses of the living cells are not timescale-invariant under relevant biological conditions [85]. There is a discrepancy between the loss behaviour measured for CSK experimentally and the one predicted by SGR model. In addition, this model was not able to differentiate between the above and below glass transition states [86]. It neither takes into account the molecular details nor does it consider the active contraction of the cells [87]. It also fails to explain the strain stiffening or the cell rheological behaviour at high frequencies [88]-[90].

V. Biphasic Continua

All the continuum models discussed earlier considered the cytoplasm as a single phase material, either solid or liquid, whereas the biphasic model views it as a two-phase material, a combination of both solid and liquid phase [91] as depicted in Fig. 6.

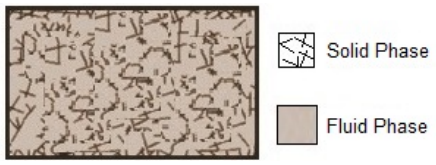

Fig. 6 The schematic representation of the bi-phasic model of the cytoplasm illustrating the solid phase (consisting of CSK, organelles, and macromolecules) and the fluid phase (consisting of cytosol)

A. Biphasic Poroelastic Models

In this continuum mixture theory approaches, the solid phase of the cytoplasm is treated as linear elastic solid and the fluid phase is treated as a non-viscous fluid [92] and described as

$$\sigma^s = -\emptyset^s pI + \lambda_s tr(\varepsilon) I + 2\mu_s \varepsilon$$
$$\sigma^f = -\emptyset^f pI \quad (8)$$

where the superscripts s and f denote the solid and fluid phases, respectively, σ is the Cauchy stress tensor, ε is the Cauchy's infinitesimal strain tensor, I is the identity tensor, p is the fluid pressure, ϕ^s and ϕ^f denote the solid and fluid volumetric fractions, respectively (where $\phi^s + \phi^f = 1$), and λ_s and μ_s are the Lamé constants for the solid phase [91]. For this model, the liquid phase can emanate through the solid phase and the momentum exchange between these two phases is in the form of friction, which could be the reason for the viscoelastic behaviour of cells and tissues [31].

The chondrocytes are usually modelled as biphasic when their response to the deformation (mechanical loading) is simulated using the multi-scale modelling approach [93]-[99]. The pressure that actuates the blebbing process is not equally distributed across the cell, but generated and used locally. This is in accordance with the hypothesis of a poroelastic cytoplasm [100]. It has been demonstrated that the passive aspiration of the neutrophil inside a micropipette can be described by the biphasic poroelastic model [101]. Recently, it has been experimentally evident that this model can define the cell rheological properties at short time scales [102]. This model has also been implemented in 3-D computational simulation of pericellular matrix [103], [104]. In conjunction with other standard models, it can define the biphasic responses of cartilage [105].

In addition to the complexity of the governing equations of continuum mixture theory, the irregularity of the cell shapes make the analytical solution along with the computational modelling of this model very complicated [54]. It predicts neither the complete creep response of the chondrocytes to a step aspiration [106] nor their initial deformation behaviour under compression [107]. In addition, it disregards the plasma membrane [92].

B. Biphasic Poro-Viscoelastic Models

The biphasic poro-viscoelastic model was introduced to capture the time-dependent responses of the chondrocytes both in full and partial micropipette aspiration experiments [106], [108]. This model can be further extended to triphasic model by entailing the ionic phase. This can be achieved by precise coupling of mechanical, chemical, and electrical events [91].

VI. Active Continua

This class of models has an ability to incorporate the inherent active nature of the living cells and measure their material characteristics.

A. Bio-Chemo-Mechanical Model

This biochemical and mechanical model has been proposed to simulate the force dependent assembly and disassembly of Stress Fibers (SFs) and Focal Adhesions (FAs) by incorporating the dynamic reorganization of the CSK [6]. This model elucidates the biochemistry of SF remodelling along with a biomechanical description of SF contractility. The biochemistry of SF formation is based on two key experimental observations; SFs assemble due to activation of signalling molecules and they dissociate on reduction in tension in CSK [109]. The mechanical response of the single SF remodelling consists of three coupled phenomena and these are employed in this model using simple phenomenological relations as follows

a) An Activation Signal that Triggers the Formation of SFs

For this model, generally an exponentially decaying signal is presumed based on experimental observation. The activation signal can be expressed by dimensionless signal

intensity C

$$C = exp(-t_i/\theta) \quad (9)$$

Here t_i is the time measured from the onset of the i^{th} activation signal and θ is the decay constant of the signal [6].

b) The SF Formation Rate Dependent on the Activation Signal, Coupled with Their Dissociation Rate Affected by the Tension in the CSK

The first-order kinetic equation describing the rate of SF assembly and disassembly is given by

$$\frac{d\eta}{dt} = \left[(1-\eta)\frac{C\bar{k}_f}{\theta}\right] - \left[\left(1-\frac{T}{T_0}\right)\eta\frac{\bar{k}_b}{\theta}\right] \quad (10)$$

where η is a non-dimensional activation level that measures the extent to which the actin and myosin are incorporated into SF and $\left(\frac{d\eta}{dt}\right)$ denotes differentiation with respect to time t measured from the instant of application of the first signal. The term T is the tension in SF and T_0 is the isometric tension considered to be directly proportional to the activation level η and expressed as $T_0 = \eta T_{max}$, where T_{max} is the isometric tension in SF at maximum activation level ($\eta = 1$). The non-dimensional constants $\bar{k}_f$ and $\bar{k}_b$ govern the rate of formation and dissociation of the SF, respectively [110].

The first term on the right hand side in (10) delineates the rate of the SF formation; it decreases with increase in activation level η and increases with the activation signal C. The second term on the same side defines the rate of the SF dissociation; it decreases with increase in tension T in the SF and increases with the activation level η [110]. The SFs are stable at the isometric stress level, but as the stress falls below this level, they disassemble [111]. The SF assembly rate is indirectly and disassembly rate is directly dependent on stress [112].

c) The Cross-Bridge Mechanics between the Actin and the Myosin Filaments Generates the Tension in the SFs

Considering the analogy of the force generation mechanism between the SFs and muscle cells, the influence of this generated tension on the SF contraction/extension rate is embedded in a version of Hill's equation as:

$$\frac{T}{T_0} = 1 + \frac{\bar{k}_v}{\eta}\left(\frac{\dot{\varepsilon}}{\dot{\varepsilon}_0}\right) \quad (11)$$

where $\dot{\varepsilon}$ is the strain rate, $\dot{\varepsilon}_0$ is the maximum strain rate, and the dimensionless Hill type constant $\bar{k}_v$ describes the reduction in tension due to the strain rate [110]. The fast shortening rate provides the maximum rate of SF disassembly resulting in the reduction in tension and finally, the cell reaches a steady-state level of contraction [44]. This constitutive description of the cell includes both the active contribution from the actin SFs and the passive elastic contribution from the intermediate filaments (IFs) and the microtubules (MTs) [6]. The results of parallel-microplates technique for myoblast subjected to compression were found to be in good accordance with this stress-strain relationship [113].

The rigidity of the sites where the cell is attached to the substrate governs the concentration of SFs through orientation distribution of isometric stress. This model predicts that for stiffer attachments to the substrate the orientation of isometric stress is more anisotropic and subsequently, the concentration of SFs is higher [6] as illustrated in Fig. 7 (a) and (b).

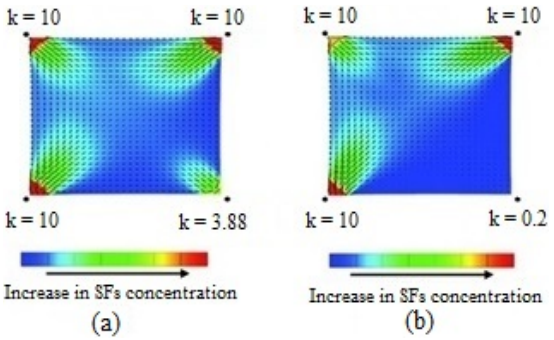

Fig. 7 Results of computational simulations predicting the effect of reduction in the stiffness of support. Here, all the supports have equal stiffness k = 10, except the bottom right support in (a) k = 3.88 and (b) k = 0.2. The contours of SFs concentration have been plotted along with the line segments representing the direction of maximum principal stress (modified from [6])

This model is able to capture the coupling mechanism arising from cell-substrate interaction and intracellular machinery. It predicts the influence of substrate compliance on the cellular traction forces in 2-D simulation of cell on micro-needles [114]. In addition, this model is able to describe the influence of variegated stiffness and architecture of the substrates on the cell behaviour. It has been demonstrated that cells adherent to stiffer substrates exert higher traction forces and simultaneously form more prominent FAs and SFs [115].

In conjunction with mixed-mode implementation of the FA assembly model, this model predicts the cell response to the substrate stiffness in 3-D application and the results obtained are in line with the experimental observations [116]. This model is not only able to predict the spatial distribution of traction forces but also the decrease in the force generated by the cell with increasing substrate compliance; this is in accordance with the experimental observations [110].

The kinetic model of the SF formation and disassociation (10) has been incorporated with force-dependent model for the assembly of FA. The new-coupled model has been employed to elucidate the experimental observations of dispositions of SFs and FAs at the periphery of convex ligand patterns. It also predicts the high concentration of FAs along the edges of cells on the V-shaped ligand pattern as depicted in Fig. 8 (a) and the enhanced formation of highly aligned SFs along the non-adherent edges as illustrated in Fig. 8 (b) [117]. The same model has been implemented to investigate the relationship between the cytoskeletal contractile forces and FA dynamics [111].

This model is able to predict the changes in SF orientation and assembly for the 2-D cells subjected to the cyclic uniaxial

stretch. It has been demonstrated in the simulation that the stress-generated perpendicular to the direction of stretch is greater than the stress generated in parallel and is consistent with the higher actin polymerization levels in the same direction [118]. This model has also been employed in simulations of 1-D and 2-D cell migration to evaluate the spatial distribution of traction forces [119].

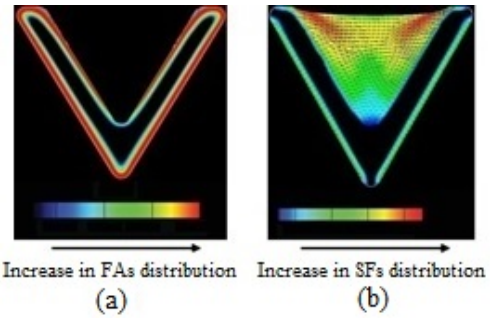

Fig. 8 The predictions of (a) FAs concentration and (b) SFs distribution in computational simulation for a cell on the V-shaped ligand pattern (modified from [11])

The bio-chemo-mechanical model has been refined to include a signalling model based on the messenger molecules used in signal transduction [120]. The implementation of active formulation in 3-D simulations has demonstrated remarkable difference in the stress distribution in cytoplasm and nucleus compared to the simulation with the conventional passive material models [116], [121].

Overall, this model is able to simulate the responses of cells to a wide range of loading scenarios. On the other hand, this model neither includes the FAs explicitly nor the biomechanical behaviour of MTs and IFs. This model has assumed space independent activation of the signal for 2-D and 3-D applications [52].

VII. Isostatic Model

An isostatic model has been proposed because the classical theory of elasticity was not able to explain the channelled long-distance force propagation phenomenon [7]. This model has proposed a framework for the CSK network based on the continuous isostaticity theory that has been developed in [122]-[124]. This model is based on the concept that the focused propagation of force stimuli in the framework over large-distances and the "action at a distance" effect is feasible only when the considerable parts of the CSK network are isostatic [7].

Isostatic structures belong to the class of statistically determinate systems (for a given external loading and boundary conditions) [125]. Due to the peculiar structure of an isostatic network, the force in an individual structural member of the network can be deduced from equations of equilibrium and geometrical properties of the network without considering the constitutive equations of structural members [123]. It is noteworthy, that such partial differential equation of stress field is hyperbolic in nature and can predict the long-distance stress propagation over specified directions [7], [125].

Several conditions are described for the isostaticity of CSK network. In scenario A, all nodes of the CSK network can support torques, which is in accordance with the assumption of open-foam cell model that has been proposed in [27], [126]. This situation may occur when the forces applied to the cell are not sufficient to buckle the filaments. In scenario B, only some of the nodes of the CSK network can support torques. This situation appears when all filaments that are converging at a node carry tensile forces (representing microfilaments (MFs) and IFs) except a single filament, that may carry compressive forces (representing MT). Lastly, in scenario C, in the limit where none of the nodes of the CSK network supports torques the structure behaves like tensegrity [15], [127]. Through the cytoskeletal remodeling process, the cell can propagate the mechanical signals to some regions of the cytoplasm, while blocking them in other regions. Thus, the CSK network could be viewed as partially isostatic [7], [125].

This model is able to predict the relationship between the long-distance force transfer and the cytoskeletal prestress. The prestress in the network can be regulated via tightening or loosening of filaments that causes three effects on the isostatic CSK network as explained in the following cases. In the first case, no filament is tightened or slacken and because of this, the CSK network will remain isostatic and there will be either negligible or no effect on the force transmission. In the second case, loose filaments are tightened. This adds a number of force-bearing elements in the CSK network thus making the CSK to lose its isostaticity by becoming statically undetermined. Because of this force, transmission within the network will be scattered and weakened over short distances. In the third case, tight filaments are slackened this reduces the number of force-bearing elements in the CSK network making the system unstable and lose its isostatic properties. As a repercussion, force-transmission via these loose filaments will not be possible and they will disperse [7]. This observation is in line with the experimental findings of disrupted long-distance force transmission in airway smooth muscle cells [128].

The novel framework proposed by this model is independent of the structurally defined pathways (like SFs) to describe the force transmission in cells, thus they can describe how cells transmit forces in 3-D extracellular matrix (ECM) and in cells adhering to 2-D soft substrates. On the contrary, the concept of isostaticity is strongly dependent on the distribution of the tensed filaments (representing MFs and IFs) and compressive filaments (representing MTs) in the CSK network, but so far, there is no experimental evidence for such force distribution in living cells. The hyperbolic field equation proposed by this model is true only when the network achieves its marginal stability, this may not be the case for the CSK network in living cells, which constantly changes and reorganizes its structure [7].

VIII. Limitations and Future Scope

The continuum approach ignores the contribution of molecular structures that form CSK by considering them too

small compared to the size of cell. Thus, this approach does not provide an explanation for how to modulate the cell functions via mechanical forces [54]. The multi-scale model, [129] that would bridge the gap between the continuum approaches and the microstructural approaches could be one of the solutions to overcome this limitation. These models could be devised by precise coupling of simulation results from individual length scales [30], [31].

The structural model of single cell mechanics should be universal, such that it accurately predicts the responses of all cell types for all loading scenarios. The model should entail not only the physical structure and organization of distinct cell types, but also the changes in them during any cell cycle. In addition, it should also account for all cellular processes and timescales [130]. For computational simulations of a wide variety of single cell experiments, the constitutive formulation involving molecular processes should be implemented [52].

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