Biomechanics of cells and subcellular components: A comprehensive review of computational models and applications

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Abstract

Cells are a fundamental structural, functional and biological unit for all living organisms. Up till now, considerable efforts have been made to study the responses of single cells and subcellular components to an external load, and understand the biophysics underlying cell rheology, mechanotransduction and cell functions using experimental and in-silico approaches. In the last decade, computational simulation has become increasingly attractive due to its critical role in interpreting experimental data, analysing complex cellular/subcellular structures, facilitating diagnostic designs and therapeutic techniques, and developing biomimetic materials. Despite the significant progress, developing comprehensive and accurate models of living cells remains a grand challenge in the 21st century. To understand current state of the art, this review summarises and classifies the vast array of computational biomechanical models for cells. The article covers the cellular components at multi-spatial levels, i.e., protein polymers, subcellular components, whole cells and the systems with scale beyond a cell. In addition to the comprehensive review of the topic, this article also provides new insights into the future prospects of developing integrated, active and high-fidelity cell models that are multiscale, multi-physics and multi-disciplinary in nature. This review will be beneficial for the researchers in modelling the biomechanics of subcellular components, cells and multiple cell systems and understanding the cell functions and biological processes from the perspective of cell mechanics.

Keywords: protein filaments, subcellular components, cells, systems beyond a cell, biomechanical models

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1 | INTRODUCTION

Cells are the building blocks of life and specifically, the fundamental component of tissues. Their dynamic and active features endow them with the inherent ability to mutate in accordance with their functional states and respond to external stimuli in terms of cell movement, contraction, polarity and enzyme production. [1] A broad range of biological processes depends crucially on the phenotypes of cells and subcellular components, e.g., stiffness, morphology, architecture, and dynamics. Hence, numerous experimental investigations have been reported in the literature,[1-2] which cut across several spatiotemporal scales into those characteristics, such as the measurement of the flexural rigidity of filaments [3], identification of the role of actin cortex architecture in the regulation of cell surface tension [4] and exploration of the relationship between the number of signalling molecules and cell polarity. [5]

Despite the advantages of experimental studies, the importance of *in-silico* mathematical frameworks and/or models cannot be overemphasized as they facilitate better interpretation of experimental data and provide further insights into the phenomena and/or complex interrelationships that remain challenging for current experimental techniques. It is understood that both the experimental techniques and computational modelling can span over multiple scales.[2, 6] However, the latter is more efficient in quantifying the impacts of multi-components or different factors at various spatial and temporal scales. So far, several excellent reviews[1,2,7-10] have been reported in the literature, which include the computational models at different spatial scales and for a range of biological processes and characteristics. For instance, Mogilner[7] provided a review on the development of cellular protrusion models, the reviews by Danuser, Mak and their co-workers [8-9] were centred on cell migration while Rodriguez and co-workers explored various experimental and modelling approaches available for the biomechanics of whole cells.[1] An interesting review on intercellular regulation was presented by Mak et al. [2] and Alt and colleagues provided an extensive review on the vertex models of multiple cells for cell mechanics and tissue morphogenesis.[10]

The available literature reviews so far are primarily focused on cell models designed to understand particular cell functions or biological processes. Some subcellular models for individual protein filaments or their networks and whole cell models constructed recently to explore the mechanotransduction process, are not covered despite their essential role in studying the biomechanics of hierarchical cells that are involved in a wide range of pathological and physiological processes. The present article thus aims to provide a comprehensive summary of the computational modelling techniques from the level of protein polymers to subcellular level, cellular level and the spatial scales beyond a cell. In addition to the concise model descriptions, this review also provides further information in terms of the functions and applications of the models and thus offers valuable guidance for the development and applications of an integrated, active and high-fidelity cell model.

To provide an appropriate context to the present review, the cellular structures are illustrated in FIGURE 1. The upper left inset in the figure shows the nanoscale protein filaments, including an F-actin filament and a microtubule (MT). A bunch of these protein filaments form the microscale F-actin network (the upper right inset) and the star-shaped MT network (central FIGURE 1), which are woven together to establish the cytoskeleton, a larger protein filament scaffold submerged in cytosol (central FIGURE 1). The cytoskeleton plays a central role in maintaining the cell shape and stiffness, and regulating cell rheological properties. It not only melds multiple subcellular components into a whole cell (the lower left inset), but also provides the cell-cell and cell-extracellular matrix (ECM) connections in a multicellular system (the lower right inset). The cytoskeleton can sense the changes in ECM stiffness and external forces, and convert the mechanical signals into biochemical/physical ones to excite electrochemical activities in cells, i.e., cell mechanotransduction. Specifically, the protein filaments of the cytoskeleton frequently grow (the protein polymerization) or shrink (the protein depolymerization) due to biochemical/physical stimuli, which enables cytoskeleton remodelling to facilitate cell polarity, i.e., changes in cell shape and structure, and cell motility, e.g., protrusion and adhesion at cell leading edge and deadhesion at the cell body and rear.

In this article, a series of cellular/subcellular models are reviewed in sequence according to their ascending spatial scales. Firstly, the modelling techniques for the nanoscale protein filaments are summarised, including F-actin filament and MT. This is followed by the models for the microscale F-actin and MT networks. Subsequently, the review is focused on whole-cell models and finally, models with scale beyond a cell, where the cytoskeleton is the central subcellular component. The outlook for the future prospect of cellular models is discussed at the end of the paper.

2 | PROTEIN FILAMENT MODELS

The nanoscale protein filaments are the building blocks of the microscale cytoskeleton and thus are responsible for cell shape, structure and physical properties. In addition to F-actin filaments and MTs mentioned above in FIGURE 1, there is another type of protein filaments in the cytoskeleton, i.e., intermediate filaments (IFs), along with a host of adaptors, regulators, molecular motors, and other structural proteins [11]. In this section, a comprehensive review is conducted on the biomechanics models of the nanoscale protein filament, i.e., F-actin filaments and MTs as well as IFs.

2.1 | Actin filaments (F-actin)

F-actin filaments are long filamentous protein polymers acting as basic structural components in the cytoskeleton of eukaryotic cells. [12-13] Owing to their unique structures, F-actins possess the ability to perform a broad range of essential cellular functions in cell motility as well as in locating and transporting protein complexes in cells. [14] Herein, the biomechanical models of individual F-actin filaments are categorised into the subsections below in terms of the biophysical activities and biomechanical responses they characterize. The schematics of some typical biomechanical models developed for individual protein filaments are shown in FIGURE 2.

2.1.1 Force generation via protein polymerization

In cell crawling, an F-actin filament in the vicinity of the membrane grows via the protein polymerization, and thus pushes the membrane in front of it to generate the protrusion at the leading edge of the cell. In an attempt to study the force generation during the cell motility, Peskin et.al., developed an active model for an F-actin, i.e., the Brownian ratchet model (FIGURE 2(a)).[15] This model was created based on the understanding that chemical reactions rectify the Brownian motion, which leads to the polymerization or growth of F-actin and thus, generates membrane protrusive forces via the ratchet mechanism, i.e., the intercalation of the protein monomers between the membrane and the protein polymer tip.

A few years later, Mogilner and Oster [16-17] put forward the rigid polymerization ratchet theory for rectified diffusion to the situation where the polymerizing filaments are flexible so that their thermal fluctuations are sufficient to create a monomer-sized gap to permit polymerization. This model was able to identify the dependency of the load-velocity relationship for the elastic Brownian ratchet, and the optimal filament angle, on the length of the filaments and the magnitude of the applied force. Further modifications were made to the model (e.g., the end-tracking motor model [18]) to better understand the rapid elongation and substantial force generation by cytoskeletal filaments. In the end-tracking motor model, the filament end-tracking proteins advance on filament ends to facilitate rapid elongation and force generation by persistently tethering filaments. The motors consuming considerable energy, advance by means of hydrolysis-driven affinity-modulated interactions.

2.1.2 Correlation between mechanics and 3D configuration

Until 1995, analyses of the mechanical properties of actin have largely relied on simple homogeneous cylinder models. However, a vast range of potential motions and flexibilities of F-actin may be due to the unique three-dimensional (3D) configurations. It is therefore necessary to develop the modelling techniques able to reflect the 3D configuration of F-actin filaments. To address these issues, a normal mode analysis (NMA) model [19] that captured the dynamical spectral of F-actin was developed. Herein,

a short segment of F-actin was modelled with a highly simplified representation without considering any internal flexibility in the actin monomer. Numerical simulations based on this model proceed from the atomic level to the filament level. Relying on a single fitting parameter, the model can reproduce various experimental results, including persistence lengths, elastic moduli and contact energies. A wormlike chain (WLC) model was employed in a bid to describe the dynamic or thermal fluctuation responses of actin. [20-21] The WLC model represents the protein polymer as a differentiable space curve and can characterise the conformations of the polymer chains by quantifying the distribution function of end-to-end distance.

To overcome the limitation of the existing modelling techniques on the size of F-actin, Ming et al.[22] developed an analytical method called the substructure synthesis method (SSM). The basic concept of the SSM model is to treat the motions of a given structure as a collection of the motions available for an assemblage of substructures. The choice of substructures is arbitrary and sometimes quite natural, such as domains, subunits, or even large segments of biomolecular complexes. In another article, the authors also employed the SSM simulation method to analyse the vibration of F-actin filaments whose length ranges from 2 to 128 substructures (4.6 μm).[23]

2.1.3 Impacts of the structural details on the mechanical responses

Up till the year 2005, it remained challenging to delineate the effect of detailed structures in subdomains of actin on the structural and mechanical properties of F-actin. To resolve this issue, Chu and Voth [24-25] utilized the molecular dynamics (MD) simulation and the coarse-grained molecular dynamics (CGMD) method to elucidate the influences of atomic monomer conformation (FIGURE 2(b)). In the MD simulations, the trajectories of atoms and molecules are determined by numerically solving Newton's equations of motion for a system of interacting particles, where the forces between the particles and their potential energies are calculated using interatomic potentials or molecular mechanics force fields.

The CGMD models were developed aiming to increase the temporal scale by treating small groups of atoms as single particles. In Chu and Voth's studies, each actin monomer is coarse-grained into four particles, and each particle corresponds to one of the subdomains of the actin monomer. The coarse-grained particles are joined to construct the biomechanical model of F-actin filament. The temporal scale at which the molecular structure changes due to atomic motion is negligible during the investigation into, e.g., macroscopic stiffness. This model can determine the persistence length of F-actin and relate the conformation of the DNase I-binding loop (a subdomain of G-actin) and the intermonomer interactions.

Several years later, the MD simulation was also utilized by Matsushita and co-workers [26] to evaluate the extensional and torsional stiffness of F-actin. It is worth mentioning that a multi-scale model with the combination of MD and NMA was also developed by Deriu and colleagues to further explore the relationship between the mechanics of F-actin and its molecular architecture.[27] Subsequently, the CGMD method was used to identify the unique mechanical properties of F-actin due to G-actin subunit structural difference. [28-30]

To account for the helical structure of F-actins, Yamaoka and Adachi [31] developed the Cosserat continuum model of an F-actin by considering the F-actin as an elastic rod with mismatch between centroid and central axis. Such a mismatched structure can lead to the coupling between the axial stretch and bending deformation, and the axial stretch and twisting deformation. Very recently, the molecular structural mechanics (MSM) model for F-actin was developed by Li et al.,[32] where the interacting protein monomers were modelled as an elastic beam and the stiffnesses of the beam are calculated based on the force constants of the monomer interaction measured in MD simulations. The model can reveal the effect of helicity on the mechanics of F-actin and characterising the reinforcing effect of the actin-binding proteins on single F-actin.

The MSM was employed to predict the mechanical properties of F-actin. The obtained Young's modulus (1.92 GPa), torsional rigidity (2.36×10^{-26} Nm^2) and flexural rigidity (10.84×10^{-26} Nm^2) were

found to be in good agreement with the experimental data. The tension-induced bending was also observed for F-actins as a result of their helical structure. In addition, structure instability was studied for the F-actins in filopodial protrusion by considering the reinforcing effect of the actin-binding proteins. The predicted buckling load agreed well with the experimental data (~1 pN), showing a pivotal role of the actin-binding protein in regulating the stiffness of F-actin bundles during the formation of filopodia protrusion.

2.1.4 F-actin nucleation

As reviewed above, a vast amount of effort has been devoted to studying force generation process and the correlation between the biomechanics and conformations and/or structure of F-actin. The process of spontaneous nucleation however was still not well understood. Therefore, Sept and McCammon explored the thermodynamics and kinetics of F-actin nucleation with a Brownian dynamics (BD) model.[33] The basis of the BD simulations is the solution of the equation that relates the position of the protein, diffusion constant, time step and temperature. The model was applied to obtain the binding-free energies of the structures along the nucleation pathway. Such a BD model was also used to investigate the remodelling processes of actin dynamics. [34]

2.2 | Microtubules (MTs)

In addition to F-actin filaments (Section 2.1), MTs are another protein filaments that serve as a major structural element and primary organizer in the cytoskeleton of eukaryotic cells.[35] These protein filaments form ‘‘tracks’’ on which motor proteins transport organelles. They can also construct the spindle apparatus to facilitate cell division.[36] In particular, MTs are responsible for resisting compression to maintain the shape of and provide rigidity to the cells. Another unique feature observed is the dynamic instability of MTs, i.e., MTs switch between growing (or polymerization of the proteins in cytosol) and shrinking (or depolymerization of the proteins in MTs) phases.

2.2.1 Force-velocity relation in protein polymerization

Similar to the research on the force generation due to actin polymerization, the force-velocity relationship during the polymerization of MTs also attracted the considerable attention of pioneering researchers. Dogterom and Yurke [37] measured the force-velocity relation for a single MT and explored the mechanism of MT polymerization based on a ratchet model. [15] Later, the Ratchet model was refined by Mogilner and Oster [38] to delineate the growth of MTs by considering the "subsidy effect" arising from the fact that an MT consists of 13 protofilaments (PFs). The model can predict the length-dependent growth rate of and the force generated by MT polymerization (or MT growth), and estimate the MT-driven deformation of liposomes observed in experiments.

2.2.2 Modelling on the biomechanical responses

Lattice models were developed for MTs to study their vibration, buckling and thermal fluctuation of MTs, the major topics of great interest in the biomechanics of MTs. Chrétien and co-workers [39-40] gave a precise description of MT structures in terms of a surface lattice composed of tubulin monomers in the one-dimensional lattice accommodation model. Inspired by the lattice model, a two-dimensional (2D) lattice model for MT vibration was developed by Portet et al. [41], where the dimers are modelled as mass points at their centres of mass. The pitch of helices that run around the MT wall is proportional to the equilibrium distance between adjacent dimers along a PF. This model can predict the vibration dispersion relations as well as wave propagation velocities and relate the vibration frequencies and wave propagation velocities with the elastic constants and the geometrical characteristics of MTs.

Continuum mechanics models were obtained for MTs based on the assumptions that the MTs are made of a homogeneous elastic material. These models were used to analyse experimental results on MTs. [3, 42-43] Several theoretical studies were also conducted to explore the biomechanical responses of MTs, which however remains challenging for existing experimental techniques. To characterise the acoustic vibration behaviour of MTs, a 3D mechanics model was developed by Sirenko et al., [44] which is equivalent to a cylindrical membrane shell model where the bending stiffness of MTs is neglected.

In addition, the ideal fluid flow model was employed in the reference [44] where the vibration was studied for MTs submerged in a liquid. The 3D mechanics model [44] can derive the eigenfrequencies and eigenmodes of individual MTs and those submerged in cytosol, but some errors were introduced due to the above-mentioned simplifications.

Inspired by this pioneering work, Ru and co-workers have developed an elastic orthotropic shell model (FIGURE 2(c)) [45-49] and a beam model [50]. The beam model for MT was also employed in the works by Gao, Lei and Li. [51-52] The orthotropic shell model is able to account for the bending stiffness and the high anisotropy of MTs, which are essential in studying buckling and vibration of MTs. Combined with the theory of nanomechanics, these models can characterise the small scale-effect on MT mechanics, such as non-local effect and size-effect. For example, the continuum models were developed to reveal the influence of the geometric size on the buckling of MTs. [53-56]

The structural details of MTs may exert significant influence on the mechanical behaviour and properties of MTs. However, these details are missing in the continuum mechanics models. To overcome this limitation, the MD simulations were performed by Deriu and colleagues [57] to acquire the monomeric information of MTs and a mesoscale spring model was proposed based on the information obtained. Four years later, based on Deriu's work, Ji and Feng [58-59] developed a CG mechanochemical model to study the dynamic behaviour of MTs, where the interactions of tubulins are taken into account from the molecular basis. The proposed model enables one to characterise the conformations of sheet-ended MTs, the structural evolution and to simulate the radial indentation process of an MT. In addition, an anisotropic elastic network model with the combination of MD and NMA was also developed by Deriu et al., [60] for studying MT mechanics. This technique shows higher computational efficiency than does MD, which enables it to describe a protein system of hundreds of tubulin monomers. The overall mechanical properties of MTs, such as bending stiffness, Young's modulus, and persistence length can therefore be estimated with higher accuracy based on the model.[60]

The WLC model developed for F-actin was extended to the study of MT mechanics. In 2008, the

WLC model was utilized by Taute et al., [61] to study the dynamics of thermal fluctuations of MTs. A worm-like bundle (WLB) model [62] was also developed, which accounts for the discrete character of the internal architecture of the MT as a bundle of PFs and its internal deformations. Unlike the WLC model, the WLB model exhibits a state-dependent bending stiffness due to the generic competition between the bending and twist stiffness of individual filaments and their relative motion mediated by the stiffness of the crosslinkers. The model is able to correlate the effective bending rigidity of MTs to the number of constituent PFs.

Over the past decade, attempts have been made to develop MT models able to capture the more detailed features of MTs at a lower computational cost or with higher efficiency. Coupled atomistic-continuum models thus were obtained for MTs. In 2011, an atomistic-continuum model was developed for global buckling of MTs, which was also used to study MT vibration. [63-64] In this model, the material properties and continuum energy are evaluated based on atomic interactions. It overcame the previous limitation on computational size without losing the information about inter-atomic interaction.

In 2014, an MSM model developed by Zhang and Wang [65] was used to measure the mechanical properties of MTs. The technique established the equivalency between the deformations of the structure of MTs and the structural frame representation of MTs. Its robustness and efficiency have been demonstrated in studying the mechanical responses of MTs such as vibration and buckling.[43, 66-70] Specifically, the MSM models with monomeric feature were employed to identify the origin of the inter-PF sliding and its role in bending and vibration of MTs. [43] A 3D transverse vibration was reported for MTs, where the bending axis of the cross-section rotates along the longitudinal direction and each half-wave oscillates in different planes.[68] The MSM model was also used to explore the subcellular environment effect on the MT mechanics and reveal the physics of the experimentally observed localized buckling as well as the role of the cross-linker in determining MT stiffness.[69] Moreover, studies were carried out using the MSM model for MT vibration excited by an alternating external electric field which provides useful guidance to the development of the MT-based biosensors.[71-72]

2.3 | Intermediate filaments (IFs)

In eucaryotic cells, IFs are also a major component of the cytoskeleton. However, the modelling effort is relatively scarce on exploring IF as compared with the models developed for MTs (Section 2.1) and F-actins (Section 2.2). IFs are crucial in defining key biomechanical functions of cells such as cell migration, cell division and mechanotransduction. These protein polymers are also referred to as the ‘‘safety belts of cells’’ as they can protect cells by avoiding exceedingly large stretch.[73-75] The MD and CG models (FIGURE 2(d)) were employed by Qin and co-workers [76] and quantitatively compared with experimental data in studying IF biomechanics. The models are capable of characterising the responses of the IF to mechanical stretching. Specifically, they have introduced a new paradigm from an atomistic perspective in studying the biological and mechanical properties of IFs, which lays the foundation for understanding the pathway of protein molecules to impact at larger length-scales.

3 | MODELS OF CYTOSKELETAL NETWORKS

In Section 2, the models developed for the nanoscale protein filaments of the cytoskeleton, i.e., F-actin filaments, MTs and IFs, are reviewed. Herein, the focus of review is transferred to the microscale networks of the protein filaments, i.e., actin network (Section 3.1), MT bundle (Section 3.2), IF network (Section 3.3) and MT combined with F-actin (Section 3.4). These networks of protein filaments are the structural elements of the cytoskeleton and thus have numerous functions within the context of cell and cytoskeleton mechanics. Typical examples are their pivotal role in forming anchoring points between the ECM and the cell membrane, and their contribution to maintaining cell shape as actin cortex. [77-78] It thus is of strategic importance to achieve accurate and robust models for the subcellular structures like actin network. [79]

3.1 | Actin network

3.1.1 | Elastic responses and properties

Initially, the energy-based description approach was favoured by the researchers in the study of the actin network. In 1995, MacKintosh et al. [80] developed an energy-based model for crosslinked gels and sterically entangled solutions of semiflexible biopolymers to bring in new insights into the elastic properties of *in vitro* actin networks. Their work showed the dependence of elastic properties of the actin network on the concentration of actin solution. One year later, also with an energy description of biopolymer, a WLC model was employed by Kroy and Frey [81] to study the entanglement transition and plateau modulus of actin networks.

The WLC description was further used by Gardel et al. [77] to examine the role of entropic effects in network elasticity and correlate the mechanical properties of individual filaments to the overall elastic behaviour of the whole network. Also, based on the WLC description, Palmer and Boyce [82] proposed a microstructurally-informed continuum mechanics model to explore the stress-strain relation of the network. Later in 2011, the concept of WLC description enabled Broedersz and MacKintosh [83] to generate a phantom network model and examine the effects of motor protein generated forces on the mechanics of actin networks. Following the approach of Palmer and Boyce [82], Unterberger et al. [84] developed a micro-sphere model for cross-linked actin network where the well-known WLC model was used to represent individual actin filaments. This model provided a stable framework for solving more complex boundary-value problems, such as the simulation of AFM tip indentation on the cell membrane.

In 2003, a discrete network models of rigid rods (i.e., the F-actin filaments were considered as rigid rods) was utilized by Head et al.[85-86] to study the elastic reponses of the F-actin network. Two regimes of elastic responses was identified as the functions of cross-link density and filament rigidity. The first one is characterized by affine deformation and filament stretch and compress, and the second one by nonaffine deformation and bending of the cross-linked networks. In the same year, the rigid

network model was further utilized by Wilhelm and Frey [87] to characterise the scaling regimes of elasticity. A novel intermediate scaling regime was identified, where the elastic response is dominated by bending deformations. FIGURE 3 illustrates the schematic representations for a few discrete models developed for the F-actin network as well as MT bundle and cross-linked MTs and F-actin filaments. A rigid rod model shown in FIGURE 3(a) was applied to the study of the stress generation by myosin minifilaments in the random action network [88]. More recently, the effect of F-actin length changes on cortex tension [4] was also investigated by using the rigid rod model.

The network models of elastic rods (i.e., the filaments are treated as elastic rods) were also developed and used to study the mechanical responses of actin networks. In 2005, the transition from a bending-dominated response at small strains to a stretching-dominated response of large strain was explored by Onck et al. [89] based on a 2D network model of filaments as elastic rods. Furthermore, Roy and Qi [90] developed a micromechanical model to predict the average macroscopic elastic properties of the actin network. In their model, the actin-network was represented by a unit cell consisting of four semiflexible chains and four equivalent axial-bending springs. The proposed unit-cell-based micromechanical model represents a statistically average realization of the actual network and gives the average mechanical properties, such as the shear modulus, for the actin network.

3.1.2 | Strain hardening process

When subjected to deformation, the actin network experiences a strain hardening process which enhances the energy required for further deformation.[91] A open cell foam model was developed to characterise such a strain hardening response. [92] In 1997, using the open cell foam model,[93-94] Satcher et al.[95] described the deformation of the actin networks induced by filament bending, twisting and sliding. In this model, the actin network is described as a structure consisting of beamlike components connected by rigid cross-linkers. The shape of the network is either cuboid, dodecahedron, tetrakaidecahedron, or icosahedron, and its stress is primarily generated from the bending and twisting of the component struts. Based on this model, the mechanical properties of the actin network were

computed and compared with experimental results. The strain hardening under compression was also predicted by using the model for the adherent cells exposed to local mechanical perturbations. [92] The models for strain-stiffening characterisation have been further elaborated to account for non-affine deformation of actin networks. In 2007, Huisman et al. [79] took the initiative to study the mechanical responses of the actin network subjected to a large strain. The simulation technique was employed, where the actin network was modelled as a discrete 3D system consisting of cross-linked beam.

A cross-linked beam model was developed by Huisman et al.[79] and is shown in FIGURE 3 (b). The networks are generated by a procedure inspired by MD and deformed using an updated-Lagrangian finite element (FE) model of beams. This model revealed the relationship between the 3D network architecture and the non-affine behaviour of the actin network. In 2008, Åström et al. [96-97] developed an elastic network model where Euler-Bernoulli beam is used to represent the segments and the spring model is employed to describe the cross-links between them. In the simulations, the stiffness matrix method was used, which enabled the authors to explore the strain hardening as well as other behaviours of the actin network including avalanches of cross-link slippage and spontaneous formation of stress-carrying fibre bundles.

In combination with the WLC model, Huisman et al. [98-101] used a Monte Carlo scheme to generate thermalized networks. Starting from a random, isotropic network, Monte Carlo simulations were performed to alter the topology of the network and minimize its free energy. Subsequently, the segments are cut until a required average filament length is obtained. This operation finally results in a disordered network of curved filaments. The model was efficiently used in studying, e.g., the nonlinear stiffening behaviour and non-affine bending regime of the actin network.

3.1.3 | Dynamic behaviours

The dynamic behaviours of actin networks such as growth, shrinkage, symmetry-breaking and structure remodelling have also attracted adequate attention due to their crucial role in cellular activities. A coarse-grained (CG) Monte Carlo model was utilized by Kang et al.[102] to simulate the

response of the network under cyclic stretching. The model has, in principle, the advantage of studying how mechanical stimulation changes actin cytoskeleton structure and influences dynamic responses.

The Monte Carlo technique was also incorporated into the network models to simulate other active performances, e.g., the microscopic dynamic model obtained by Wang and Wolynes.[103] This model can simulate active contractility that combines the motor-driven stochastic processes with the response of individual F-actin to asymmetric load. A finite-element based discrete network model was also developed, which was combined with stochastic crosslink scission kinetics [104] to account for the rate-sensitive stiffening-to-softening transition in F-actin networks induced by crosslink unbinding.

The growth of actin networks plays a critical role in the crawling mobility of almost all eukaryotic cells, and it also provides the force required to extend cell protrusions (e.g., lamellipodia) and to propel intracellular pathogens (e.g., Listeria) through the cytoplasm. [105-106] In this process associated with filamentous polymerization, individual F-actin filaments in the networks can be modelled as dynamic 'ratchet'. [15-17] For example, van Oudenaarden and Theriot [107] developed a stochastic model for actin network, in which F-actin filaments are modelled as elastic Brownian ratchets. The model was used to quantitatively characterise the experimentally observed emergent symmetry-breaking behaviour. Years later, the authors further developed the model into a 'tethered ratchet' model, [108] which can explore the responses of the actin network when their filaments are attached to a surface transiently.

In addition to the ratchet models, other models were also achieved, aiming to study the dynamic behaviours of actin networks. In 2001, to simulate the growth of branched actin networks against obstacles, Carlsson [105, 109] developed an 'autocatalytic branching' model. It assumes that filaments branch off the sides or ends of existent filaments with the rate proportional to the number of the existing filaments. This model captures the correlation between the load force and the protrusion velocity.

After this, in 2004 Alberts and Odell [110] developed a 'nano-propulsion' model to study Listeria propulsion in realistic 3D geometry by numerically simulating every filament and all microscopic mechanical interactions in the comet-like actin tail. The authors modelled the molecular mechanics of

the growth/disassembly of an actin network as it interacts with a moving rod-shaped bacterium. This *in-silico* reconstitution can produce persistent bacterial motion and actin tail morphology, and explains how the observed 'runs-and-pauses' movements can emerge from a cooperative binding and breaking of the attachments between F-actin and the bacterium.

In 2012, a hybrid mesoscopic model for actin-based propulsion was established by Zhu and Mogilner [111] to explain the observed bistability of the orientation of the ellipsoidal beads propelled by actin tails. The model incorporated both arrays of dynamic F-actin at the surface-tail interface and the bulk deformable actin gel behind the interface. It can also explain both the concave-up and concave-down force-velocity relations for the growing actin networks depending on the characteristic time scale and network recoil.

3.1.4 | Pre-stress effect and mechanotransduction

The behaviours of cells under the influence of the cell-generated forces have always been an intriguing topic in exploring cellular nature. Such forces can drive changes in cell shape and ECM remodelling, and contribute to the control of cell growth and functions, as well as tissue patterning and mechanotransduction at the organ level. [112-113] The pre-stress existing in the actin networks is an example, which exerts influence on cell phenotype and cell functions. As a result, significant effort has been made to develop the network modelling technique able to reveal the pre-stress effect. Such a pre-stress is believed to be generated via cell contraction or distension on the substrate. [114]

In 2003, Coughlin and Stamenović [114] applied a prestressed cable network model [115-116] to the actin network to characterise its deformability. The network model consists of tensile cable elements (linear-elastic springs) without the balanced compression in the MTs. The model can measure the elastic properties of cells. Another type of prestressed network model is the tensegrity model, [115, 117] which was applied by Luo et al. [118] to predict mechanical behaviours of actin networks. In the tensegrity model, an actin network is treated as a discrete scaffold of self-stabilizing pre-stressed components.

Herein, tension is taken by F-actin filaments and balanced by the compression withstood locally by MTs. All the pre-stressed components are subjected to mechanical equilibrium and geometric deformation. The mechanical behaviours that can be characterised by this model include viscoelastic retraction, fibre splaying after severing, non-uniform contraction, etc.

Mechanotransduction is a process in which the protein filament network senses a force and transmits it to cellular transducers (e.g., the nucleus, membrane, and cell-EMC adhesions) where the force will be amplified and converted to biochemical signals. The conversion of physical forces into biochemical/physical information is fundamental to the development of physiology. [119] It provides a simple means by which cells and organisms can ensure structural stability, as well as a way to regulate morphogenetic movements for precise three-dimensional structure generation.[119] Actin network plays an essential role in the mechanotransduction of cells.

To examine this issue, Shafrir and Forgacs [120] constructed a model for the actin network, where the F-actin filaments are considered as rigid rods connected with springs. The model was used to study the mechanotransduction process in cells subjected to either shock wave-like or periodic mechanical perturbations. The energy transfer was also investigated for the actin network in this study. Later in 2012, Zeng et al. [121] developed a 3D actin network model consisting of randomly distributed linear Hookean springs. The model was used to represent the cytoskeleton in cells and predict the deformation of the nucleus due to the stresses transmitted and magnified from the plasma membrane to the nucleus membrane via the cytoskeleton.

3.1.5 | Actin network remodelling

Remodelling of the actin network is essential in implementing cellular functions during various physiological and pathological processes. This leads to the reorientation of individual actin-filaments, the reorganisation of the network and the phenotypic changes of whole cells. To study the turnover and orientation of actin stress fibres (SFs) in the actin network, a kinematic model was obtained by Kaunas

and Hsu, [122-123] which enabled the authors (1) to describe experimentally observed time courses of SF reorientation to the direction perpendicular to the cyclic uniaxial stretch, and (2) to account for the lack of alignment in response to an equiaxial stretch.

In the same year, a form finding model for the F-actin network was proposed by Gong et al. [124] to explore the response of the F-actin network under stretching. The analyses are carried out based on the nonlinear large deformation FE analysis. Herein, the beam and cable elements are used to model F-actin and their cross-linkers. This model can predict experimental observations of filament re-orientation, and evaluate the effects of the filament relative density, the filament length, and the relative density of filament cross-linkers on the elastic modulus of the network.

The 2D network model of randomly oriented springs was also used to study the network mechanical responses. A 2D model [125] was used to correlate the active self-organization of the actin network to its stiffness and the traction forces generated by the network. The model thus allows one to examine the responses of adherent cells to stretch and substrate stiffness change. In 2014, a CGMD model developed earlier for the actin network [126] was employed by Li et al. [127] to reveal the mechanisms of the responses of the F-actin network subjected to compression. The model has the advantage of explaining the crosslinker unbinding mechanism dominated in the network deformation and disclosing the dependency of network response on strain rate. Rrecently, a multiscale FE model was developed by Klinge et al. [128] to account for the actin network-cytosol interaction. This model can be used to study the filament orientation and its influence on the biomechanics of the actin network.

3.1.7 | Rheology of the actin network

Cellular rheology is one of the subfields in cell biomechanics and largely determined by the cytoskeleton where the actin network is the major component. It has captured considerable attention due to its important role in accomplishing the biological functions such as angiogenesis, wound healing and disinfection.

To study the rheology of the actin networks, researchers have proposed a wide range of

computational models. In 2007, Kroy and Glaser [129-130] introduced a glassy WLC model that was obtained by adding the exponential stretching of the relaxation spectrum of its long-wavelength eigenmodes to the original WLC model. The model can predict the dynamic structure factor of the actin network and show that its microrheological susceptibility exhibit the characteristics of soft glassy rheology. The results obtained compared favourably with experimental data for reconstituted cytoskeletal networks and live cells.

Another example is the cross-link-governed dynamics model which uses a combination of Monte Carlo simulations and an analytical approach [131]. The model can characterise long-time network relaxation controlled by cross-link dynamics. This is done by describing the structural relaxation resulting from many independent unbinding or rebinding events. A more detailed review of cytoskeletal rheology can be found in the reference,[132] which brings together the experimental methods, theoretical models and computational techniques used in studying cytoskeletal rheology.

3.1.8 | Special issues on the actin network

In addition to the aforementioned models, there also exist a variety of network models focusing on some special issues which can serve as references for the development of future modelling techniques. For instance, the BD utilized in the modelling of single filaments was also used in the study of the actin network morphology. Kim et al. [133-134] studied actin-related phenomena by using the BD simulation model, e.g., (1) the effects of system parameters on the growth and morphology of the network, and (2) the role of unbinding and unfolding of actin cross-linking proteins in determining their dynamic properties. Following Kim's research, Borau and co-workers [135] proposed a 3D model with the same foundation of the BD model. The authors performed the simulations to study the active cross-linked actin networks as the force generator and force sensors of the extracellular environment.

In 2013, an MD model was used by Alvarado et al. [136] to examine the hypothesis that the stress-dependent binding kinetics allows motor activity to degrade initially well-connected networks to a critically connected state. A year later, Alonso et al. [137] proposed a particle-based model for the network

based on the flocking theory, which can be recognised as a distributed Kelvin-Voigt particle model. This model can characterise strain hardening, viscoelastic creep, stress relaxation, rupture and reformation of the actin network. Combination of the viscoelastic Kelvin-Voigt element with the cross-bridge cycle of myosin motors leads to a Kelvin-Voigt-Myosin model [138], showing the dependence of cell fluidization on the stretching protocol, i.e., the stretch-compress or compress-stretch manoeuvres.

Later, a thermodynamically consistent constitutive model was proposed by Fallqvist and Kroon [139] to explore the correlation between the microstructure and mechanical behaviour of the networks. The model efficiently captured many experimentally observed characteristics of the actin network including strain hardening, network rupture with subsequent softening and viscoelastic deformation. Here, it is worth mentioning that molecular proteins, e.g., the cross-linking proteins of protein filaments[133-136] and the myosin motors[83,136,138], have an important role to play in determining the mechanical responses and bio-functions of cytoskeletal network.

Here, it is worth mentioning that molecular proteins, e.g., the cross-linking proteins and the myosin motors, have an important role in determining the mechanical responses and bio-functions of the cytoskeletal networks. In various discrete models of the cytoskeletal networks the cross-linking proteins were modelled as the geometrical connections of F-actin,[85, 86] rigid bodies,[95] elastic springs,[96, 97, 120] and cable elements,[124] respectively. The results showed substantial influence of the cross-linking proteins on elastic responses/properties,[85,86] strain hardening effects,[95-97] dynamics behaviour,[101] mechiancanotransduction[120] and network remodelling.[124] Specifically, the spatial and angular orientation of the two filament binding sites, size, stiffness and cross-linking density were identified as the important attributes of the cross-linking proteins to the mechanical deformation of the protein filament networks.[133, 136] The role of the myosin motors was also studied based on the mechanical models of actin networks [83, 88] showing that the motor protein generated force exert substantial influence on the mechanical response and properties of the actin networks. Moreover, the pathway of myosin motors to contract the cross-linked filament networks was revealed[136] and the sensitivity of the

myosin detachment rate to the tension of the network was examined as the cause for the asymmetric behavior of the stress fibers.[138]

3.2 | MT bundle

The studies of MT and IF networks are relatively scarce as compared with the intense focus on modelling of actin networks. MTs are essential components of the cytoskeleton as the network/bundle of MTs plays important roles in providing cell stiffness, intracellular organization and cell morphogenesis, and facilitating cell division, cell motility and intracellular cargo transport. Furthermore, a variety of neurological functions are also mediated by the MT bundles, such as maintaining the mechanical integrity and shape of the axon and promoting axonal growth [140-141]. Therefore, the modelling of MT mechanics is of interest to cell mechanics researchers.

Buxton et al. [142] developed a stochastic model of the MT network, which can not only describe the mechanics and kinetics of individual MTs, but also characterise the diffusion of tubulin and tau concentrations. It thus can reflect the effects of tau concentration and the hydrolysis of GTP-tubulin to GDP-tubulin. MT dynamic instability can therefore be modelled based on the stochastic model.[142] Another noteworthy example is the bead-spring model (FIGURE 3c). It was used by Peter and Mofrad [143] in studying the mechanical behaviour of axonal MT bundles in tension. The model can capture the details of stiffening behaviour of an MT bundle in tension and identify its primary deformation modes.

A few years later, Allain and Kervrann [144] used particles to describe a network of discretized but connected MTs and simulated the network dynamics using Newtonian mechanics theory. To represent the rigidity of MTs, equivalent elastic forces acting on individual nodes were evaluated based on Euler Bernoulli beam theory. The model accounts for the coupling between cytosol and MT dynamics in a constant state space and thus enables the use of data assimilation techniques.

3.3 | IF network

The cell-specific IF network is often pictured as an integrator of F-actin filaments and MTs via a complex set of cross bridging proteins [145]. Each specific IF network can integrate the cytoskeletal system of cells into tissues and organs [145]. Ackbarow et al. [146] modelled a larger-scale deformation of an IF network based on a coarse-grained multi-scale model of alpha-helical protein domains. The characteristic properties of the networks were corelated to the nanomechanical properties of their protein constituents to identify the role of the proteins in protecting the network against catastrophic failure. Bertaud et al. [147] also obtained an empirical coarse-grained computational model of the IF network in eukaryotic cells. The study approximated the nonlinear force-extension behaviour of IFs under tension by a multilinear model. This work revealed the significant role of IFs in controlling the mechanical responses of cells subjected to large deformation and brought in the mechanistic insight into cell deformation under varying IF densities.

3.4 | MT combined with F-actin

Researchers have attempted to model the MTs linked with F-actin which possess the ability to sustain tension and compression, and thus, offers the rigidity and structural stability of cells. [148] In general, it is known that in the cytoskeleton, F-actin filaments undergo tension while MTs resist compression. [148] In 2011, Mehrbod and Mofrad [56] proposed a model for cross-linked MTs and F-actins (FIGURE 3d). The overall configuration of the F-actin-MT connection resembles the deck-main cable connection in a suspension bridge. The model can simulate the semi-discrete loading pattern that mimics the filamentous environment around the MTs and thus distinguishes it from a continuum environment. [149]

3.5 | Other models for the cross-linked networks

In addition to the models reviewed above, there is another group of models developed to capture the fundamental physics, e.g., the percolation and structure-property relations of the cross-linked network.

These models are beneficial to researchers in studying the mechanical responses or mechanical-chemical processes of the cytoskeletal networks although they originally were not developed for one specific type of the cytoskeletal networks.

The effective medium network approach was proposed by Feng et al., [150] for disordered, semiflexible polymer networks. The technique gives a reasonable overall description of the dilute elastic systems consisting of Hooke springs. It can be used to find the distinct elastic regimes of semiflexible filamentous networks, in which the contributions from filament bending or stretching to the macroscopic modulus vanish.[151] These techniques and their results can provide useful guidance for the study of the biomechanics of cytoskeletal networks consisting of protein polymer.

The percolation theory was established for the interconnected or cross-linked network, which was employed by Forgacs[152] in biological system to examine the role of cytoskeletal filamentous networks in intracellular mechanical-chemical signalling. The connectivity of the cytoskeleton was studied based on the model, which is found to be essential in determining the mechanical behaviour of adherent cells. Motivated by the dynamics of the cytoskeleton, a hydrodynamic model of active gels [153-154] was developed, which was employed to characterise the spontaneous dynamical behaviour of topological singularities, such as disclinations (asters and vortices) in 2D. The model was further extended to the problem of cell locomotion on a substrate. Efforts were also made to form the connection between the hydrodynamic models and the microscopic motor dynamics.[155]

A continuum nonlinear elastic model of the affine-network[156] was developed, which accounts for the strain stiffening in a range of distinct biopolymer gels formed from cytoskeletal and extracellular proteins. A stochastic "motor-clutch" model proposed by Chan and Odde [157] for fibrous network is capable of simulating how cytoskeleton senses environmental stiffness to control cell shape, migration, and fate of filamentous systems. In addition, newly developed models, such as the BD-FE model [158-159] of Brownian dynamics of polymer and the Lattice-based dilution model [160] of fibrous networks can also be efficiently used in studying the biomechanical responses of the cytoskeletal networks.

4 | WHOLE CELL MODELS

After the review on the models for the nanoscale protein filaments and the microscale networks of the protein filaments, this section is devoted to the review of the biomechanical models for single cells. Living cells in the human body are constantly subjected to mechanical stimuli throughout their lives. The stresses and strains can arise from both the external environmental and internal physiological conditions. Therefore, major research efforts have been directed to quantitatively evaluating the mechanical responses and properties of cells subjected to stimulations or perturbations in cell motility, signalling and shape changing. One of the earliest attempts to mathematically describe cell deformation is the use of continuum mechanics models with assumed constitutive relations, e.g., viscoelastic model. The illustrations of some typical whole-cell models are shown in FIGURE 4.

4.1 | Constitutive relation of cells

In early stage, cells are modelled as a bio-system made of one or a few homogeneous materials with different constitutive relationships. The details of cell structures and subcellular components were not considered. Herein, the efforts made to reveal the constitutive relation of cells are summarised below.

4.1.1 | Solid-phase models

In 1981, a solid-phase model (FIGURE 4(a)) was proposed by Schmid-Schonbein et al. [161] to study the small-strain deformation of human leukocytes undergoing micropipette aspiration. The cells are modelled as homogeneous material with viscoelastic constitutive relation. Theret et al. [162] developed a simplified viscoelastic material model to understand micropipette aspiration of cells. The model was capable of predicting the stiffness of endothelial cells exposed to shear stress. This viscoelastic model can also describe one-dimensional locomotion based on a system of differential equations governing cell deformation, displacement and adhesion-receptor dynamics.[163]

Other viscoelastic models are also available in the literature for the study of cell mechanics during,

e.g., uniaxial extension and relaxation.[132, 164-165] After these, cell models with different constitutive relations were proposed, including a hyper elastic model for large deformation response [164] and a poroelastic model for the networks where the pores are filled with a viscous fluid. [164, 166-167]

In addition to the theoretical models, FE simulation was performed based on the viscoelastic constitutive relation to evaluate experimentally measured *in vivo* and *in vitro* force levels in cells, and examine their effects on cell mechanics.[168] Mijailovich et al. [169] also utilized a FE model to predict cell deformation in the virtual experiment of magnetic bead twisting. Herein, the relationships were obtained between the torque applied to the cell and the resulting cell deformation, bead rotation, and lateral bead translation. The FE constitutive modelling techniques (FIGURE 4(b)) were further employed in studying (i) nematode sperm crawl,[170] (ii) eukaryotic cells adherent to a substrate, [171] (iii) the mechanotransduction pathway during endothelial cell rounding,[172] (iv) the cytoskeletal rheology and protrusive activity [173] and (v) the mechanical role of each cytoskeleton component under loading. [174] The relationship between softening of F-actin/IF layers and 3D cell deformation was also investigated via the FE simulations.

4.1.2 | Multiple-phase models

Besides the one phase solid models, some multiphase FE models were developed for cell mechanics, where a cell was thought to be made of the materials of different states. [168, 175] A typical example can be found in the study carried out by He and Dembo on sea urchin cells.[176] In this work, the authors treated a sea urchin cell as a composite consisting of two materials: the gel-like or viscous cortex and the watery interior fluid. Such a multiphase model was capable of describing the "fully deformable 3D free boundary problem for cell shape in cytokinesis". [176] These biphasic models were fitted into experimental data to obtain the intrinsic material properties of a cell attached to a rigid substrate. [177]

In addition to the mechanical responses, the multiphasic models were also employed to study (i) the mechanotransduction of the chondrocytes and the mechanobiology of the cartilage,[178-179] (ii) integrate the contractile stress, F-actin, and cytosol flow with traction forces, [180] (iii) examine the

dependency of cell contraction on the stiffness of the extracellular environment and (iv) accurately reproduce the formation process of an oriented SF network observed in contracting fibroblasts. [181]

4.1.3 | Liquid-phase models

In some cases, cells behave like a liquid drop and adopt a spherical shape when suspended. The liquid drop models were therefore developed to simulate the flow in a liquid-like state of cell by assuming different fluid types. Dong et al. [182] applied the Maxwell liquid drop model in the study of the small deformation and the recovery behaviour of leukocytes in micropipette aspiration. Their model for a passive leukocyte consists of a prestressed cortical shell and a Maxwell fluid inside the shell. Later, a Newtonian liquid drop model was developed by Yeung and Evans [183] to simulate the flow of leukocytes deforming continuously into a micropipette. Then in 1993, a shear-thinning liquid drop model was utilized by Tsai and co-workers to investigate the dependence of the apparent cytoplasmic viscosity on the shear rate in a range of large deformation.[184]

Other liquid drop models can also be found in the literature, such as the Compound Newtonian liquid drop model proposed by Kan and colleagues. [185] The model is a refinement of the homogeneous Newtonian liquid drop model and thus, is more suitable for some non-linear phenomena. The above-mentioned modelling techniques in different theoretical frameworks are applicable in studying the mechanical responses and measuring the mechanical properties of whole cells in different scenarios. To understand the bio-functions of cells from the perspectives of cell mechanics, some specially designed modelling techniques were also achieved during the last few decades.

4.2 | Cell pre-stress and contractility

The cytoskeleton responsible for cell shape and stiffness is a network of protein filaments. These filaments are subjected to a pre-existing tensile stress that is generated actively by the contraction of the actomyosin network and passively by cellular adhesion, filament polymerization or osmotic pressure. The value of the prestress and its effects on cell shape and stiffness are thus of major interest

in the research. A well-known modelling technique to address these issues is the tensed cable network model which was introduced in the study of the cytoskeletal network. In this model,[114,116,186] the cytoskeleton was described as a network of randomly oriented cables that support a prestress. These models were used to evaluate the prestress value in the cytoskeleton and reveal the key role of the pre-stress and cytoskeleton architect in determining the elastic responses of cells.

Another modelling technique accounting for the pre-stress of cells is the tensegrity model (FIGURE 4(c)) [112, 115, 148, 168, 187-189] where the shape of the structure is stabilised by means of continuous tension rather than by continuous compression. This model can be considered as a special case of the tensed cable network model. Specifically, in the tensegrity cell model the F-actin filaments and IFs sustain the continuous tensile stress that is balanced by the local compressive stress resisted by MTs. The tensegrity cell models were efficiently used in examining a range of mechanics issues for whole cells, e.g., erythrocyte cytoskeleton at large deformation, the impact of the prestress and architecture of cytoskeleton, the role of the deformability of cytoskeletal filaments and the architectural regulation of histodifferentiation, etc.

Many cellular processes hinge on the ability of cells to exert contractile force via contraction of the actomyosin network. Contractility is essential for cells to divide, migrate, heal wounds, pump the heart and move limbs.[190] In 2002, an energetic approach[191-192] was established based on the assumption that the overall energy of a contracting cell primarily includes the contribution of the elastic substrate, the tensed actin network, and the buckled MTs. Herein, the roles of MT, F-actin and IF during cell contraction were revealed based on energy budget analysis. The bio-chemo-mechanical model for cell contractility with representative volume element was devised by Deshpande et al., [193] which accounts for the dynamic reorganization in the cell. The model is also capable of predicting some experimentally established crucial characteristics including (i) the force decrease due to the increasing compliance of cellular substrate, (ii) the influence of cell shape and boundary conditions on the anisotropy of cellular structures, and (iii) the high concentration of the SFs at the focal adhesions.

4.3 | Cell motility

Cell motility, one of the fundamental cell functions, has received considerable attention in the study of living cells. Implementation of cell motility however involves the complex interactions of signalling molecules, cytoskeleton and cell membrane, as well as the interaction between space and time. [8, 194] Numerical simulations of cell motility can achieve a wide-ranging set of goals from conceptual proof of concept to detailed biological comparisons.[194]

In 1988, a stochastic model (FIGURE 4(d)) was developed by Tranquillo et al. [195] for chemotaxis and long-term cell migration. Herein, the cell locomotion path was simulated based on the kinetic fluctuations in chemoattractant/receptor binding and quantitative predictions were made for both cell persistence time and dependence of orientation bias on gradient size.

A combined cell model for active deformation/force generation was developed by Herant et al. [196] which accounts for the active stresses and forces in the cell. The model is able to interpret and repeat the classic experiments like (i) the passive aspiration of neutrophil into a micropipette, (ii) the active extension of a pseudopod by a neutrophil exposed to a local stimulus, and (iii) the crawling of a neutrophil inside a micropipette toward a chemoattractant against a varying counter pressure.

In 2010, a level set-based, finite volume model (LSM) for cell motility was developed by Wolgemuth and Zajac.[197] The model uses the level set method to move the cell boundary and uses information stored in the distance map to construct a finite volume representation of the cell. This technique can be applied to the studies like (i) the cell motility driven by the depolymerization of the cytoskeleton and (ii) chemical signalling during chemotaxis.

4.4 | Cell polarization

Cell polarization is another fundamental feature of many cell types which need to display and maintain specialized cytoplasmic and membrane-associated domains to complete cellular biological processes,

e.g., cell differentiation, growth, division and migration, the transmission of stimuli, and the development of the immune response. [198] An immersed boundary method was used by Vanderlei et al. [199] for cell polarization and motility. The model adopts a simple reaction-diffusion system that represents the internal regulatory mechanisms controlling the polarization of a cell and determining the protrusion forces at the front of its elastic perimeter. It was used to study how protrusive and elastic forces exert influence on cell shapes, the distribution of the reaction-diffusion system in irregular domains and the coupled mechanical-chemical systems found in cells. Many cell models were obtained by considering reaction-diffusion systems, especially those for cell polarization.[200]

Another typical model for cell polarization is the combined multi-level model [201] developed by Marée et al. in 2006, which expresses protein kinetics as partial differential equations (PDE) and describes a mesoscopic cell based on a cellular potts model (CPM). The model was proposed for the polarization and movement of keratocytes. It can also describe the mutual interactions of the small G-proteins, examine their effects on capping and side-branching of F-actin, and provide insight into the response of cells to cues.

A purely thermodynamic (not involving signalling) quantitative model was proposed by Kozlov and Mogilner [202] for exploring cell polarization and bistability. The model is based on the interplay between pushing force exerted by F-actin polymerization on the cell edges, the contractile force powered by myosin II across the cell, and the elastic tension in the cell membrane. And it can calculate the thermodynamic work produced by these intracellular forces and characterise the cell mechanics by an effective energy profile on the short timescale.

Furthermore, a positive feedback model [5] was formulated to describe the stochastic effects on cell polarization. The model considered signalling molecules comprising a single species moving between non-recruiting, cytoplasmic states and recruiting, plasma-membrane-bound states without mechanisms of directed transport. Based on theis model, the relationship has been established between the polarization frequency and the number of signalling molecules.

4.5 | Cortex effect and cellular rheology

In 1994, a cortical membrane model [203] was developed based on the assumption that the stress-bearing elements of the cytoskeleton are restricted within one or several thin distinctive cortical layers where the stress balanced either completely by the pressurized cytoplasm itself, or by the cytoplasm and ECM together. This model discloses the relation between the extent of deformation curvature and the cortical thickness/resistance for bending of the membrane-cortex complex.

Later in 2001, a power-law structural damping model [204] was proposed to understand the experimentally observed rheological behaviour of the adherent cells. The model can express the complex modulus as a function of the angular frequency in a power-law and explain the dynamic behaviours that cannot readily be achieved by standard linear solid models. Another model described by the power-law description is named as soft glassy rheology model.[168, 205] It was proposed based on the observations of the resemblance of the cytoskeleton to soft glassy materials. The model is capable of explaining the macroscopic cellular response related to the localized structural rearrangements caused by meta-stability and disordered structure.

4.6 | Cell orientation, shape-change and deformability

In 2009, an active dipole model was developed by Safran and De, [206] which describes the cells that have established mature FAs and are in mechanical equilibrium with the surrounding matrix. This model is intended to capture the sum of the forces exerted by the cell via its FAs modelled as a pair of equal but oppositely directed actomyosin contraction forces. It can characterise the nonlinear dependence of cellular orientation on an external, time-varying stress field.

Ji et al. [207] developed a model based on the force-balance principles for cell protrusion. In this model, the force fluctuations were correlated with the fluctuations in F-actin turnover, flow, and F-actin-vinculin coupling. The model has successfully established the mechanistic relations between the

force development and cytoskeleton dynamics.

Particle-based models were developed for simulating the shape change of a cell due to the influence of flow and/or external forces. These include dissipative particle dynamics (DPD), smoothed particle hydrodynamics (SPH) and coupled atomistic-continuum models. In 2010, Pivkin et al.[208] applied the DPD model to study the red blood cell in microcirculation. The red blood cell was modelled as a collection of DPD particles that were immersed in a DPD fluid. The red blood cell particles interacted with the fluid particles through DPD potentials, and the temperature of the system was controlled through the DPD thermostat. The model can simulate the shape-changing processes of red blood cells in a microchannel and achieve the parachute-type shape of cells observed experimentally.

The SPH model [209-210] represents length-scales similar to continuum models, but has the advantage of being free of mesh topology constraints. Unlike DPD, SPH is derived from the Navier–Stokes equations and therefore, the parameters have clear physical meaning. The SPH model can accuratly predict the tank-treading motion of membrane and cytoplasm, and the parachute shape of the cell in flow. In a bid to account for atomistic phenomena in continuum mechanics models, a coupled atomistic-continuum (or multiscale) model for red blood cells has been developed. [211-212] In this model, human blood cells were treated as a quasi-continuum body and the the connection between the deformation of the spectrin network/cytoskeleton and that of the corresponding continuum body is established via the higher order Cauchy–Born rule. The model can capture the defomred configurations and wrinkle patterns of cells in good agreement with experiemntal observations.

Ademiloye and co-workers proposed a three-dimensional multiscale meshfree model to simulate the deformability of red blood cells parasitised by *Plasmodium falciparum*. [213-214] This model has been subsequently employed to measure the biomechanical properties of healthy blood cells in normal physiological condition [215] and when subjected to extreme loading and temperature conditions. [216-217]

4.7 | Other cell functions

In addition to aforementioned whole cell models, the phase field method was developed to simulate a diffuse interface and thus applies to cellular simulations. Such a phase field model introduced by Kockelkoren et al. [218] can simulate the response of a Dictyostelium amoeba (a unit cell organism) after the stimulation with the chemoattractant cyclic adenosine monophosphate and capture no-flux boundary conditions. The BD technique was also used in the whole-cell modelling. Luo et al.[219] developed a comprehensive, single cell-scale BD model coupled with an extensive experimental dataset of cytoskeletal distributions. In this work, the authors investigated the mechanisms that govern cytoskeletal reorganization during micropipette aspiration and decipher the cortical mechanosensing from molucule to cellular level.

5 | MODELS WITH SCALE BEYOND A CELL

Compared to the models reviewed so far in this article, the models with scale beyond a single cell enable one to efficiently investigate biological processes in the multiple-cell systems or a cell on CEM system, such as cell sorting, cell migration and cellular decision. These models can cover a wide range of biological activities and enjoy the advantage of mimicking complex biological patterns based on relatively simple rules.[2] Although many of them are difficult to reconcile with physical principles, those models can simulate emergent behaviours not easily attainable by other methods. [2] In FIGURE 5, the schematic representations are demonstrated for some of these models developed for the systems beyound single cells.

5.1 | Simulations of cell sorting

Cell sorting is the process in which a large group of one type cells are trapped inside a continous

structure of other types. It is enssential in regenerating a normal animal from the aggreates of dissociated cells of adult hydra and invovled in the rearrangement of cell position. A typical cell sorting modelling technique is the CPM, a spatial grid-based formalism that allows for mesoscopic cell description. In this model, a cell is defined over a region composed of multiple lattice sites with constraints on its area and interactions at its boundary. In 1992, Graner and Glazier [220] developed an extended CPM (FIGURE 5(a)) with area constraints and differential adhesivity. The model is capable of simulating biological cell sorting and can make detailed predictions about the measurable properties of the biological aggregates.

A decade later, the model was employed by Turner and Sherratt [221] to simulate the population of malignant cells experiencing interactions due to both homotypic and heterotypic adhesion while also secreting proteolytic enzymes and experiencing a haptotactic gradient. A year later, Ouchi and co-workers [222] modified the extended CPM to improve its correspondence to reality. The modified model becomes more accurate in predicting characteristics like the hierarchy of diffusion constants. The CPMs can also be used to study cell-based morphogenesis，[223] angiogenesis，[224] coordinated motion，[225] cell into narrow channels，[226] mechanical cell-matrix feedbacks，[227] etc.

5.2 | Modelling of angiogenesis

Angiogenesis is the process to form new vessels that enable the delivery of oxygen and nutrients to the body's tissues . It has a critical role to play in the growth, development and healing of wounds as well as cancer progression. By considering proliferation and cell movement as stochastic events, a mesoscopic lattice-based continuum model of angiogenesis [228] was developed to simulate tip cell migration, production of new vessel cells, sprouting, anastomosis and vessel regression.

In understanding tumor-induced angiogenesis, a multi-scale phase-field model was presented by Travasso et al. [229] It combines the benefits of continuum physics description and the function of

tracking individual cells. The phase-field model tracks the position of capillaries. The parameters used in the model, such as proliferation rate, cell velocity and diffusion constants can be directly related to the quantities measured experimentally. This model can identify the role of the endothelial cells' chemotactic response and proliferation rate as the key factors that tailor the neovascular network.

5.3 | Tissue morphogenesis and patterning

Tissues consist of cells that are attached to their neighbors and ECM by the cell-cell junctions and the FAs, respectively. By means of the adhesion molecules, cells in tissues can exert forces onto neighboring cells and ECM, which finally leads to the morphogenetic deformations of developing tissues. The vertex model, the off-lattice alternative of the CPM, has been used to study tissue morphogenesis and patterning.[10] This model can identify factors that are chemically relevant or cannot be explicitly expressed in terms of forces. Several formulations of the vertex models are reviewed in the reference.[10] Using the vertex model for the epithelial junctional network, Farhadifar et al. [230] investigated the influence of physical cellular properties and proliferation on the cell-packing geometries. Bi et al. [231] utilized the vertex model for confluent tissue monolayers at a constant density and demonstrated a density-independent rigidity transition in biological tissues. Also, with the vertex-based model, Coburn et al. [232] analyzed the biomechanics of epithelial cells.

A hybrid vertex/cell-centred model was developed by Mosaffa et.al.[233] to mechanically simulate planar cellular monolayers (the multicellular systems) during cell reorganization. In this model, cell centers are treated as a triangular nodal network, the cell boundaries are modelled by an associated vertex network and the two networks are coupled via a kinematic constraint. The focus of the study is on the change of cell-cell bonds due to cell reorganization or remodeling events. In 2021, using the CPM approach Carvalho et.al.[234] developed an agent-based computational model of the urothelium to describe both a healthy urothelium and the development of bladder cancer. The emphasis is placed on the identification of the conditions in which cancer cells cross, by mechanical means, the basement

membrane and invade the bladder lamina propria.

5.4 | Mechanotransduction of endothelial cells

Studies of mechanotransduction in endothelial cells were reported in the literature. In this process, the shear force on the cell apical surface due to physiological fluid flow is transmitted intracellularly and amplified at the potential transducers, e.g., the nucleus and the FAs, where the mechanical signals will be transformed into biochemical signals.

In 2007, a multi-component FEM model was developed by Ferko and co-workers [235] based on multimodal fluorescence images of confluent endothelial cell monolayers and their nuclei. The model was achieved to quantify the effects of the cellular material inhomogeneities and the discrete attachment points on intracellular stresses resulting from physiological fluid flow. It was found that the apical values of the stress/strain were amplified by 10 to 100 times in and around the nucleus, and near the FAs. Another typical example of multi-components FEM model (FIGURE 5(b)) was developed by Dabagh et al. [236] Compared with the first multi-component model, this model enables one to consider a multiple cellular system and reveals the role of more potential mechanosensors, such as glycocalyx layer, actin cortical layer, nucleus, cytoskeleton, FAs and adherent junctions in mechanotransmission and endothelial cell deformation. The FEM model in FIGURE 5(b) is the most recently developed multiple-component model and thus reflects the latest advancement in the development of multicomponent whole cell models.

5.5 | Cell's decision on cellular phenotype

Cell's decision-making is the process in which cells assume different, functionally important and heritable fates from a range of phenotypical possibilities without an associated genetic modification or environmental difference. A multiscale agent-based model for cellular decisions was presented by

Zhang et al. [237] in 2007. In this model, each cell utilizes the value state of its molecular network to 'decide' its microscopic phenotype for migration, proliferation, quiescence, or apoptosis-at every point in time. On the micro-macroscopic level, a fixed 3D lattice is employed to represent a virtual block of brain tissue, while in the molecular environment, the phenotypic behaviour of a cell is determined by the dynamical changes in the concentrations of the interacting molecular species both inside and around the tumour cells. The model can identify the effect of the overtime proliferative and migratory cell populations on the spatiotemporal expansion patterns of the entire cancer system. The agent-based model can also be applied to explore the processes like ligand clustering, integrin homo-oligomerization, integrin–ligand affinity, membrane crowdedness and ligand mobility. [238]

5.6 | Cell migration and contractility on ECM

Cell migration and cell contraction occur during many biological processes including angiogenesis and tissue morphogenesis for which the modelling techniques developed were already reviewed in Secs. 5.3 and 5.4 for multiple-cell systems. These models however are not focused on the cell migration or contraction in the two biological processes but centred on the overall effect of the fusion of all the cell functions involved or the correlation between the cell functions/properties and geometrical/physical properties of multiple-cell systems during angiogenesis and tissue morphogenesis. In the literature, there is another group of bio-mechanical models which are specially developed for the migration and contraction of cells on ECM, the fundamental cell function that plays a central role in implementing various physiological and pathological processes, e.g., wound healing, immune responses, tumor formation and metastasis, which include angiogenesis and tissue morphogenesis but are not limited to them.

In the mid-2000s, a force balancing model was developed by Zaman et al.,[239-240] to characterise the interventions due to the changes in the physical, chemical, or mechanical properties of ECM. In this model, the force balance among several components is considered and the total forces are

categorised into the traction forces on the front and the rear of the cells, the protrusion forces due to cell protrusion in the 3D matrix, and the resistive forces resulting from the viscous drag on the cell due to the ECM. This model can qualitatively predict the migration of cells in 3D matrices and determine the overall locomotion velocity vector. In 2010, the force balancing model was further extended to the study of the matrix metalloproteinases-mediated proteolysis in cell migration in 3D environments. [241]

By considering force balance between SFs and adhesion sites, an integrative cell migration model was developed by Kim et al. [242] for cell migration and spreading on fibronectin-coated planar substrates and micro-patterned geometries. Also, the concept of the stochastic events [228] used for modelling angiogenesis was further extended to the evolutionary model of tumor progression, [243] the model for the effect of migration on ECM fibrous structure [244] and the model for various cell migration features such as velocities, trajectories, cell shape and aspect ratio, cell stress or ECM displacements.[245]

In 2016, Zhu and Mogilner [246] developed a node-spring networks model where ECM is treated as a 2D node-spring network, and the cell considered is embedded in ECM. Meanwhile, an actin-myosin network inside the cell is represented by another 2D node-spring network. The model can reproduce six experimentally observed motility modes of cells, i.e., mesenchymal, chimneying, amoeboid, blebbing, finger-like protrusion and rear-squeezing cell locomotory behaviours.

More recently, a random walk-ordinary differential equation model was used by Chen et al.[247] to describe cell migration in non-isotropic fibrin networks around pancreatic tumour islets. The formulated stochastic differential equations of the model are solved via the classical Euler–Maruyama method. The simulation can explore the influence of anisotropic stromal ECM in pancreatic tumour islets T-lymphocytes migration in different immune systems.

In addition to cell migration, cells contract and change their orientation in response to the local elastic strain to maintain the mechanical homeostasis within tissue. To model the process for contractile cells, Zemel et al., [248] developed a dipole polymerization model where cells are considered as polarizable force dipoles due to the analogy between the mechanical response of the systems and the

dielectric response of polar molecules. The average cell orientation, the mean polarization stress, and the effective elastic constants of the material were evaluated as a function of the cell concentration and matrix properties.

5.7 | Cell-cell/ECM interaction

Cell-ECM and cell-cell interaction plays an essential role in determining the biomechanical responses and cell functions of the systems of multiple-cells and cells on ECM. The influence of the environmental changes, e.g., local strain/stress and stiffness change of ECM, is exerted on the cells via focal adhesion where the integrins, the transmembrane receptors connect the ECM and the cytoskeleton of cells. They serve as key sensory molecules that transduce chemical and physical cues from the ECM into biochemical signals to regulate cell behavior and functions. To understand the integrin functions, a chemo-mechanical model was developed by Paszek et al.[249] which describes the stochastic formation and the rupture of integrin bonds within a deformable cell-ECM interface. The model integrates the micro-mechanics of the cell, glycocalyx, and ECM with a simple chemical model of integrin activation and ligand interaction. It can also shed light on the effect of deformations in the cell-ECM interface on integrin clustering.

It is understood that focal adhesions made of the integrin not only bond cells and ECM but also connect adjacent cells, which enables the cell-ECM and cell-cell communications via the biochemomechanical processes and induce, e.g., cell contractility and reorientation. To characterize cell contractility and focal adhesion growth, Keshavanaravana and Ruess [250] proposed a nonlinear continuum mechanical approach considering mechanical and thermodynamic equilibrium to model the governing biochemomechanical processes involved. The governing equations of a Hill model-based stress fiber growth were provided, which were coupled to a thermodynamical approach modeling the focal adhesions.

The forces transmission between the actin cytoskeleton (or cells) and ECM or other cells are implemented via integrins where mechanosensitive protein-protein interactions is modeled as the molecular clutch.[251] Such a clutch model was recently employed to reveal the physical mechanism by which cells sense and respond to the elasticity of the ECM via integrin-based adhesions [252] and quantitatively predict how cell dynamics and mechanotransduction are controlled by molecular clutch dynamics, its master regulator and the force loading rate.[253] In addition to the cell responses to the elasticity of ECM, more recently, the clutch model was further extended to cell response to pure viscous surfaces with no elastic component. This study is important for understanding the interaction between cells and tissues that are viscoelastic in nature and their physical properties are essential in e.g., tumorigenesis and wound healing.

6 | SUMMARY AND OUTLOOK

6.1 | Modelling technique summary

Among the three major filaments of the cytoskeleton, computational research efforts have been largely directed to studying the biomechanics of F-actin and MTs. The early ratchet model developed for F-actins concentrated on simulating the force generation during the cellular protrusion by actin polymerization and the pioneering experiments explored the structure of F-actin based on the simple homogeneous assumption. Later, the normal mode analysis (NMA) model and Brownian dynamics (BD) model were also developed to reveal the behaviours of F-actin resulted from their unique 3D structure. Owing to the increase in computational capability, molecular dynamics (MD) simulations (including coarse-grained MD simulations) were introduced to study the structural and mechanical properties of F-actions, where, to improve the efficiency, the effect of detailed structures in subdomains

of actin was neglected. Later, efforts were also invested to further improve computational efficiency by developing structure mechanics techniques like substructure synthesis method (SSM) and the molecular structural mechanics (MSM) model which are suitable for large scale biomechanical modelling of whole F-actin filaments.

Similar to the research on the force generation during the cellular protrusion by actin polymerization, the force-velocity relationship during the polymerization of MTs also attracted significant attention from researchers. In these studies, the dynamical features of MTs were predicted with improved accuracy, such as the length-dependent growth rate and forces generated. Numerical investigations into fundamental mechanical responses of MTs such as vibration and buckling were carried out based on continuum mechanics models, e.g., elastic shell and beam models, and lattice or structure mechanics model, where the material properties were obtained from the atomistic simulations and experiments. Moreover, the well-known wormlike chain (WLC) model exhibited its advantage in studying the biophysics of MTs, e.g., the thermal fluctuation, and the atomistic-continuum model and MSM models enabled one to consider more details of this protein polymer at a lower computational cost. Compared with the numerous research on MTs and F-actins, modelling of IFs is relatively scarce. Among these pioneering studies are the MD and coarse-grained models of IFs, which can be used to probe the behaviour of stretched IF.

For the cytoskeletal network, the major attention has been given to modelling the mechanical responses of actin networks. Initially, the energy-based models were favoured by the researchers and used to quantify the biomechanical properties of the actin networks, e.g., elastic properties, entanglement transition and motor-generated forces. The focus of these studies was placed on a few topics including strain hardening and pre-stress effect. To name a few, the strain hardening responses were studied based on the open cell foam model, the updated-Lagrangian finite element model (FEM) and the elastic network model or the WLC model. The dynamic behaviours of the actin networks like growth and symmetry-breaking were simulated by the ratchet model, the ‘autocatalytic branching’

model or the ‘nano-propulsion’ model. In studying the pre-stress, mechanotransduction and deformation, the tensegrity model, the rigid rods model and the form finding model were developed and efficiently used.

The modelling techniques for MT network/bundles are vital for the sustenance of various biological processes but they are very few as compared with their counterparts of F-actin network. The typical examples include stochastic techniques, bead-spring model and particle-based model for the mechanics and kinetics of multiple MT structures. In addition, the IF network deformation was studied based on the coarse-grained MD model while its rheology was characterised using the Glassy WLC model and the cross-link-governed dynamics model.

Simulation of the biomechanics of whole cells has attracted considerable attention as cell mechanics play a crucial role in implementing cellular functions and processes such as protrusion, locomotion, mechanotransduction, deformation under micropipette measurements, etc. Viscoelastic model and other continuum mechanics model with FEM or meshfree methods have been widely used in modelling the mechanics of eukaryotic cells. Constitutive mechanics models like the liquid drop model and multiphasic model were also used to reflect the intrinsic features of the cell in certain aspects. To study cell dynamics, active models such as a level set-based (finite volume) model (LSM) for cell motility and cellular potts model (CPM) for cell polarization were developed, which describe a particular function of a single cell in a bid to provide new insights into a particular cellular mechanism like the response of cells to chemoattractant.

The models at the scale beyond a cell can be used to study biological processes in multicellular systems such as cell migration and cellular division. They can mimic complex biological patterns based on relatively simple rules. A well-known technique at this scale is the stochastic model including the CPM method, which has been successfully used to explore morphogenesis, angiogenesis, etc. Other common techniques like the vertex model and the force balancing model have been applied to cell migration. In addition, the collective behaviour of aggregated cells necessitates the development of

large-scale modelling techniques. For example, the simulation of cellular decisions can be achieved using a multiscale agent-based model that can 'decide' the microscopic phenotype of the cellular molecular network. Furthermore, the stochastic formation and rupture of integrin bonds within a deformable cell-ECM interface can be modelled by a chemo-mechanical model that integrates the biomechanics of the cell, glycocalyx, and ECM with a chemical description of integrin activation and ligand interaction

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6.2 | Conclusions and outlook

In the present review, it has been shown that a large number of computational models have been developed to explore the cellular nature at various spatial scales. Existing cell mechanical models however are primarily developed at one specific length scale or for certain biophysical processes. The unique features of the available models determine the 'cellular nature' they can investigate. This in turn leaves space for future efforts to develop all-around cell models that have the ability (1) to capture the interaction between cellular events across multiple temporal/spatial scales and (2) to reveal the role of cell mechanics in implementing cell functions in various physiological and pathological processes.

To achieve this ambitious goal, in future modelling work, more efforts are expected to study the biomechanics of different types of IFs as the existing models for cytoskeleton components are mainly confined to MTs, F-actin and actin networks. Subcellular components other than the protein polymers in the cytoskeleton also play a crucial role in performing a wide-ranging set of cellular functions. Thus, efforts should also be made to extend the modelling strategies developed in studying cytoskeleton filaments to the biomechanics of other subcellular components.

Furthermore, the novel integrated models incorporating the modelling techniques for different subcellular components at various spatial scales are essential in characterising the hierarchical multiscale cellular structures. This type of model can be developed by merging the existing models of individual components and provide an in-silico platform to integrate the data obtained in different

aspects and spatial levels. These novel models thus are expected to bring in new insights into how the multiscale components work in concert to implement biological functions of cells and characterise the biomechanical responses of cells in a broader range of biological phenomena. In achieving this ambitious goal, an inevitable challenge is to establish accurate models for the protein links between different components, which has not yet been explored in detail.

In contrast to other objects, living cells exhibit active responses to external mechanical stimuli, which lead to the reconstruction or remodelling of the cytoskeleton and hence, the phenotype changes of cells, e.g., the changes in cellular/subcellular morphology, structure and stiffness. The active responses are regulated or implemented via a range of biochemical and biophysical processes, such as calcium ion flow, conformational change in actin and protein movement in cells. Another future direction thus is to develop bio−chemo−physical/mechanical cell models by coupling the integrated model describing multicomponent and multiscale cellular structures with the mathematical models or atomistic simulation techniques characterising relevant biophysical and biochemical processes in cells. The coupled cell model offers an effective means to predict the interplay between the biochemical and biophysical responses, and the passive mechanical behaviour of whole cells at various spatial and temporal scales. This will be a significant step forward in the model development of cell mechanics.

Up till now, many cell mechanics models, especially the whole-cell models, remain idealised as it is a big challenge to capture the irregular configuration and complex structure of cells and subcellular components. These existing models thus are unable to reflect the phenotype changes of cells in physiological and pathological processes. This in turn limits their applications in understanding the physiological processes and facilitating disease diagnostic and therapeutic techniques. Recently, image-informed modelling techniques have been developed and efficiently used for, e.g., the musculoskeletal system and organs like breasts and hearts to construct the models with the configuration and structures nearly the same as the systems and organs studied. With the development of 3D imaging and image segmentation techniques this new strategy can be further extended to

microscale cells, subcellular components and even nanoscale protein polymers to model the cellular/subcellular structures with high fidelity. The aforementioned integrated, active and high-fidelity whole-cell models at micro/nanoscale will be a cutting-edge modelling technique for living cells and a milestone in tackling the grand challenge of cell model development in the 21st century.

Conflicts of interest

There are no conflicts to declare.

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Figures and captions

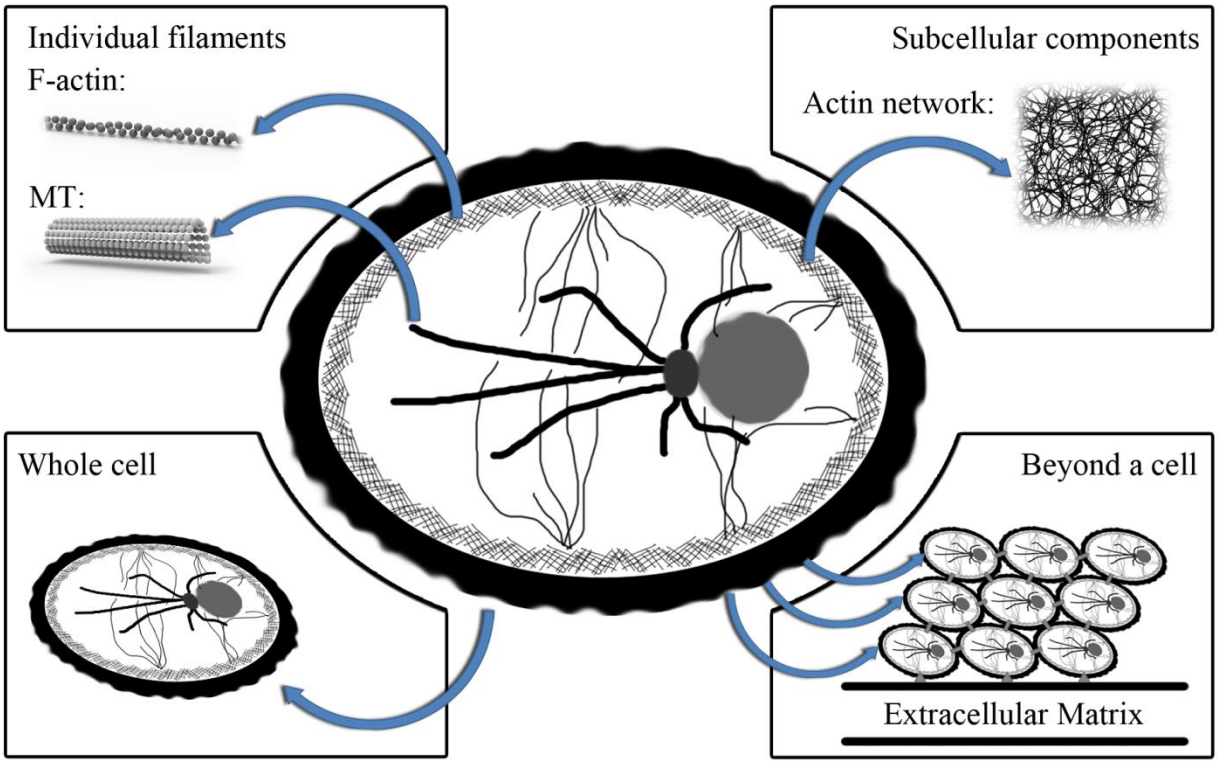
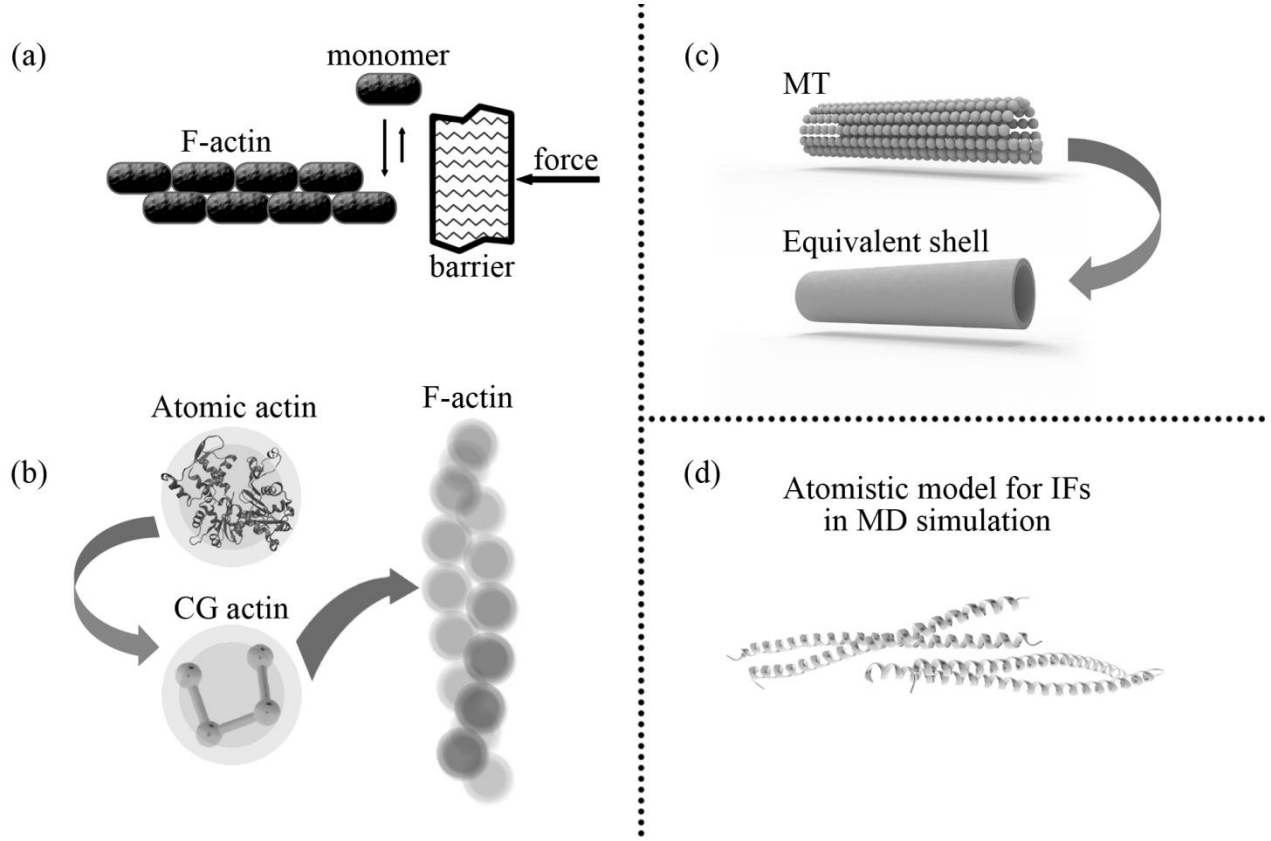


FIGURE 1 The categories for the cellular models in the present paper as individual biopolymers models, subcellular components, whole cell models and models with scale beyond a cell



FIFURE 2 The examples of schematic representations for (a) a Ratchet model of F-actin,[15] (b) an molecular dynamics (MD)/Coarse-grained molecular dynamics (CG-MD) model of F-actin, [24] (c) a Shell model of microtubule (MT) [47] and (d) an molecular dynamics (MD) model of intermediate filaments (IFs) [76]

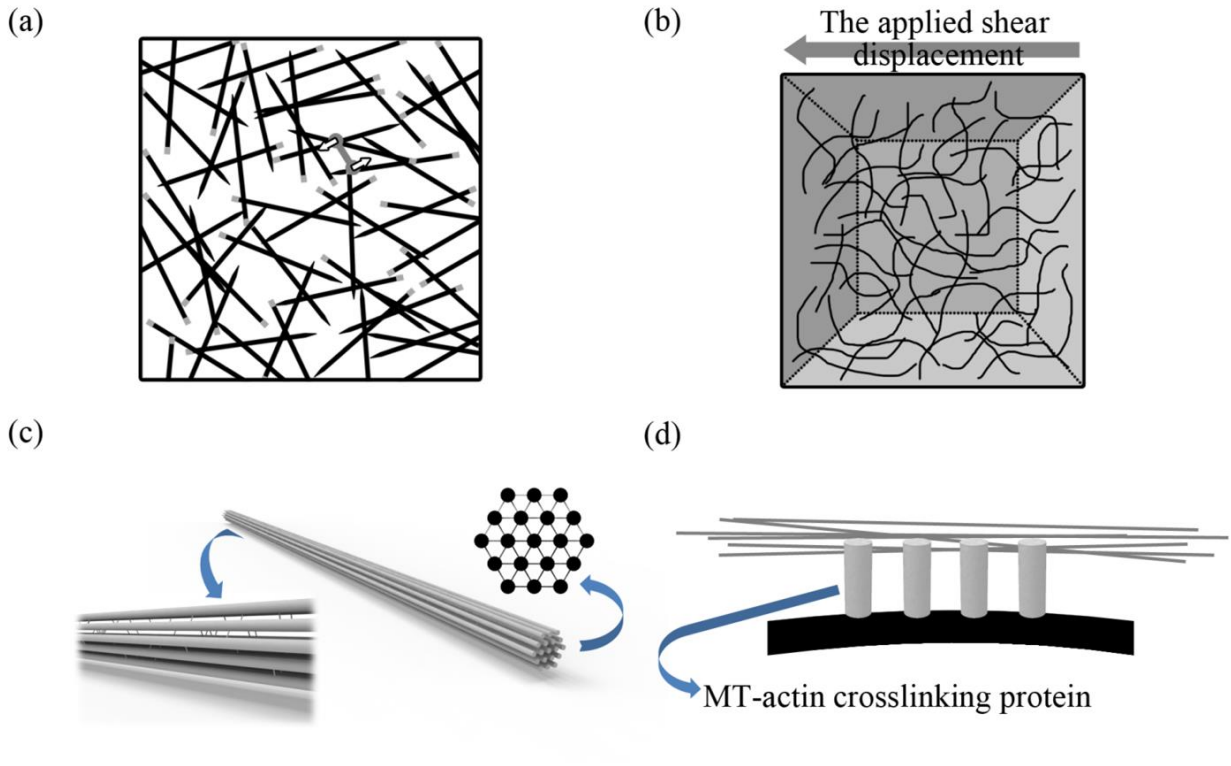


FIGURE 3 The examples of schematic representations for (a) a rigid rod model of actin network, [88] (b) an cross-linked beams model of actin network, [79] (c) a bead-spring model of microtubule (MT) bundle [143] and (d) a suspension bridge model of cross-linked microtubules (MTs) and F-actins [56]

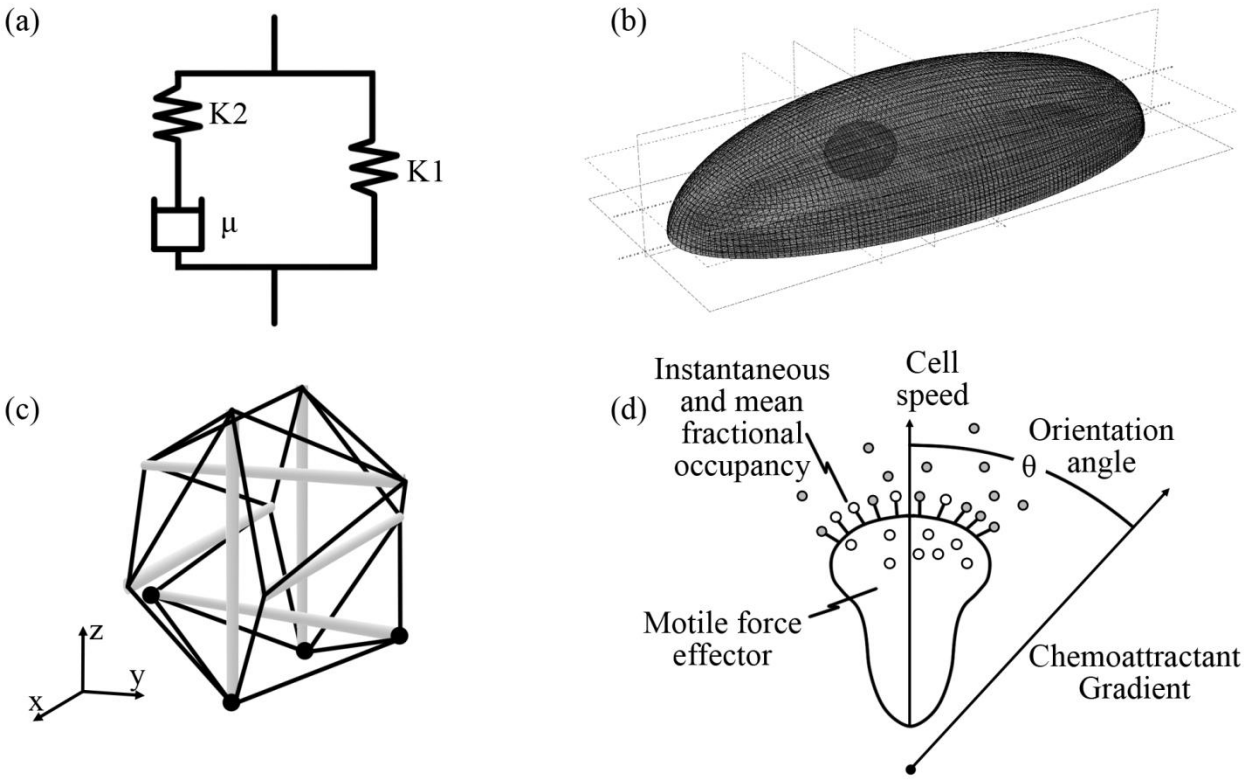


FIGURE 4 The examples of schematic representations for whole cell models (a) a viscoelastic model, [161] (b) a multi-components elastic model, [174] (c) a tensegrity model [148] and (d) a stochastic cell locomotion model. [195]

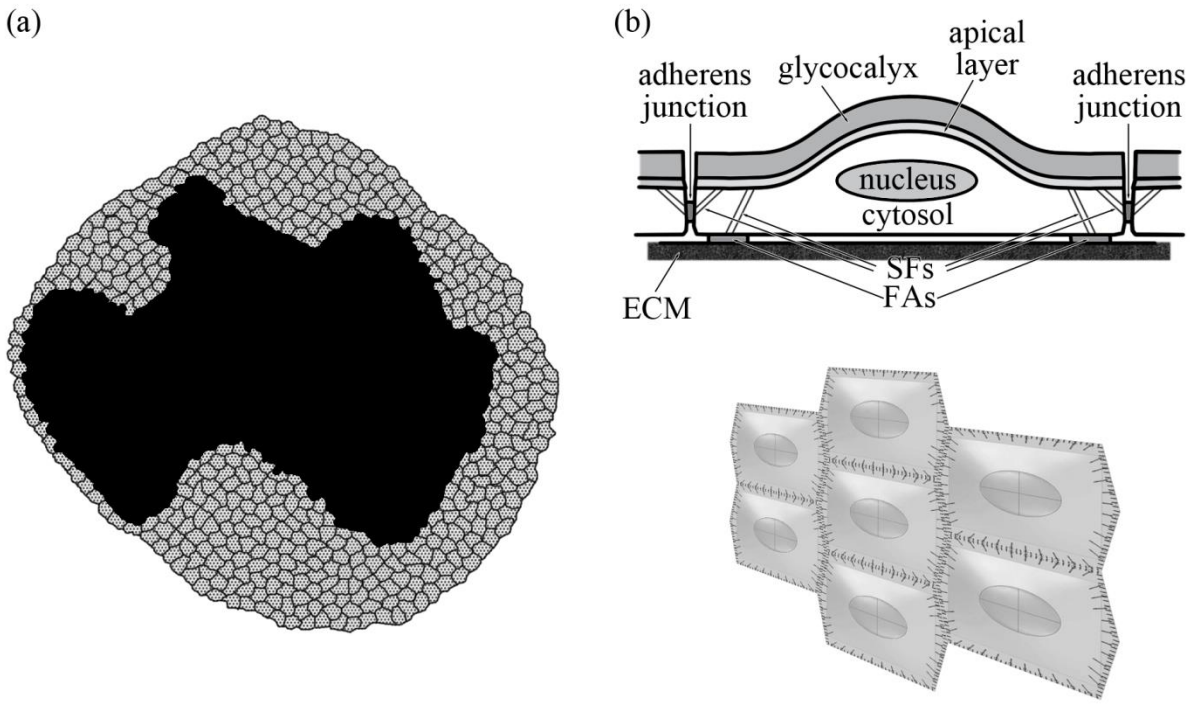


FIGURE 5 The examples of schematic representations for models with scale beyond a cell in (a) a cellular potts model (CPM) [220] and (b) a multi-component continuum mechanics model [236]