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Trans-scale Granular Modelling of Cytoskeleton: a Mini-Review

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Abstract: Living cells are the functional unit of organs that controls reactions to their exterior. However, the mechanics of living cells can be difficult to characterize due to the crypticity of their microscale structures and associated dynamic cellular processes. Fortunately, multiscale modelling provides a powerful simulation tool that can be used to study the mechanical properties of these soft hierarchical, biological systems. This paper reviews recent developments in hierarchical multiscale modeling technique that aimed at understanding cytoskeleton mechanics. Discussions are expanded with respects to cytoskeletal components including: intermediate filaments, microtubules and microfilament networks. The mechanical performance of difference cytoskeleton components are discussed with respect to their structural and material properties. Explicit granular simulation methods are adopted with different coarse-grained strategies for these cytoskeleton components and the simulation details are introduced in this review.

Keywords: Cytoskeleton, Intermediate filament, Microtubules, Microfilament network, Mechanics, Multiscale.

1 Introduction

Cells are the functional unit of living organs in various dynamic physiological behaviors. The difference between traditional material and living cell lies in the living biological features of cells [1]. The mechanical constitutive model is difficult to be extracted for living cell structures, especially at nano/microscale [2,3]. Normally, the size of eukaryotic cells is at microscale, such as osteoblasts, preosteoblasts, chondrocytes and fibroblast [4]. However, living cells is not continuum materials, but mysterious systems that consist of tremendous elaborated organelles [5].

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These non-contiguous cell structures and biological fluids surrounding them make the continuum mechanical model inadequate to capture complete mechanical properties of living cells. Several biphasic mechanics models were proposed to understand the mechanics cells based on cell aspiration experiments [6]. However, the mechanics underlying the complex biphasic model is still partly unknown as the cell structures and components are dynamically changing in physiological activities. It is crucial to understand the mechanical behavior of living cells based on the microscale cell structures. The cytoskeleton(CSK) is the structural and material foundation of living cells to undergo mechanical inputs from its surrounding living environments and validate the cell dynamics biological activities [7,8]. The CSK consists of three principal components: intermediate filaments (IFs), microtubule and microfilaments. The name of IFs is derived from its geometric properties, as the diameter is between thin microfilament and thick myosin filament [9]. IFs are involved in important tissue-specific mechanical functions in cells and tissues [10]. Microtubules are composed of α- and β-tubulin heterodimers, which attach longitudinally with each other in a head-to-tail fashion and bind laterally with a conversed stagger [11]. Microtubule is also the most rigid filament among the three important components of CSK. Microfilament networks consists of abundant actin and actin related proteins, which performs as the structural foundation in cellular dynamics [12]. These three biological filaments collaborate in living cells to provide the mechanical strength and material foundation of various cellular activities.

The understandings of the mechanical deformation of aforementioned CSK materials and structures are crucial to study the mechanical properties of living cells, which further serves the pathology study of different cell degeneration related diseases, as it is difficult to carry out in vivo experiments at microscale to investigate the mechanical properties of CSK components. Atomic force microscope can be applied at microscale for the loadings on single living cells [13]. With the development of experiment techniques in the last few decades, researchers experimentally studied the flexural rigidity and the Young's modulus of single protein filament in living cells by either directly stretching tests [14-17], or thermal fluctuation analysis [18-20]. By employing the mechanical properties from experiments, continuum beam model has been used to predict the mechanical and thermal dynamics performances protein filaments in living cells. Based on the continuum beam assumption, You et al. presented a mathematical model for the strain ampli?cation in the actin cytoskeleton of osteocytes [21], Mogilner and Oster proposed a model to explain the force generation by actin polymerization [22], Chen and Shenoy explained the myosin II induced strain stiffening of actin filament networks [23]. However, the reliability of continuum beam model being employed in the predictions on nanoscale is still unclear, and this calls for further studies. However, even if the knowledge

of single filament mechanics is available, the mechanics of complex cell structures which consist of randomly distributed materials is still difficult to be fully understood.

According to aforementioned difficulties in mechanical testing, numerical modeling method shows great potential in studying the mechanics of CSK related cell structures [24-26]. Multiscale modeling has developed in science and engineering areas such as mathematics, material science, chemistry, and fluid dynamics [27]. The multiscale modelling technique has also been applied to explain the mechanical deformation of red blood cells and normal cells [28-30], bone fracture [31], ventricular–arterial coupling during aging [32], cancer cell development [33] and bio-fluidynamics [34]. Different with single scale models, multiscale models can investigate the mechanisms of biophysical phenomena based on the physics at lower scales. Recently, molecular characterization of living cell mechanical performances provides a way to unravel the physical basis of biological phenomena in living cells [35]. In nanoscale biotechnology, the performance of protein structures is decided by its atomic configuration. With the high resolution atomic configuration of filaments [36,37], molecular dynamics (MD) simulations are executed on single actin filaments, and the structural properties are estimated [38,39]. Deriu et al. and Matsushita et al. independently studied the thermal dynamics behaviors of microfilament fragment by molecular dynamics and elastic networks model simulation, and estimated the mechanical properties of single actin filaments [40,41]. To the best of our knowledge, the study of direct MD simulations of mechanical performances of single actin filaments is limited. Regarding the computational expense of all atom molecular simulations, hierarchical multiscale modeling method is urgently needed to extend the understanding of nature optimized hierarchical structures [5,42-44].

Multiscale approaches can provide essential physical basis from atomic level biophysics analysis of protein molecules to understand biomechanics and mechanobiology of the microfilament networks [12,45,46]. At molecular level, Molecular Dynamics (MD) method can describe the ultimate motion phenomena of living systems in terms of chemistry and physics [35,47]. However, due to the limitation of computer capacity, the coarse-grained (CG) level investigation that is abstracted from all-atom MD simulations is needed to unravel the biological complexity from the physical basis. This hierarchical multiscale modeling method starts from the atomic configuration of specific proteins related to CSK and aims to model the CSK behaviors with actual cell size. Difference CG strategies are adopted based on the objective properties in modeling.

This paper mainly reviews the recent developments of hierarchical multiscale methods used for CSK modeling. The mechanical properties of different CSK compo-

nents are theoretically characterized to understand those physiological behaviors of living cells under mechanical loadings.

2 Hierarchical multiscale modelling method

The hierarchical multiscale method is a recent modeling strategy for the analysis of natural or biological systems with hierarchical structures [48]. This modeling method starts from the biophysical simulations of the nanostructures of materials right up to their macrostructures in order to understand their macroscale mechanical behaviors. Figure 1 provides the logistics of this multiscale modeling strategy and different methods that are usually adopted at different simulation levels. Up to angstrom scale, quantum mechanics calculation is needed for the analysis of interactions of the atomic configurations of the living filaments, as micro/nano scale filaments consist of various peptides. Full atom molecular dynamics (MD) method is adopted at the nanoscale level to understand the mechanical behaviors of single filaments. However, due to the computational expense of full atom simulation, coarse-grained (CG) strategies are needed to characterize the mechanical behaviors of complex networks that are built from the aforementioned nano/micro scale filaments. Based on systematic studies at all scales, the mechanics of CSK can be studied to understand the microscale mechanical behaviors of a single living cell based on molecular level simulations.

In the follow sections, modeling details of different CSK components are independently introduced. These components include Intermediate filaments, microtubule and microfilament network.

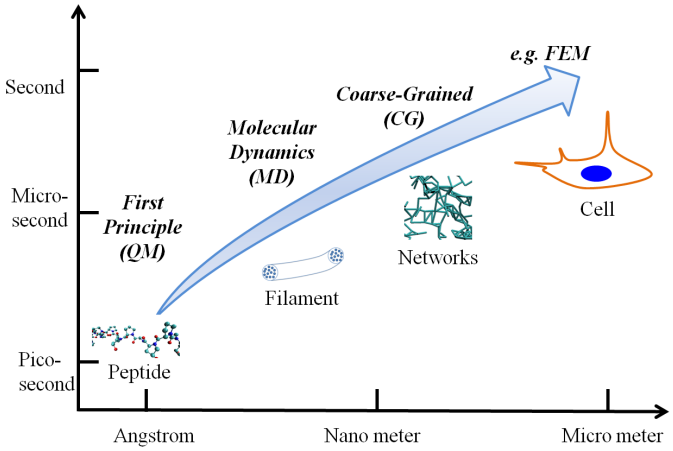

Figure 1: Hierarchical multiscale method for cell modeling.

3 Intermediate filaments modeling

3.1 Introduction of IFs

The terminology, intermediate filaments (IFs), comes from the geometric propertiesof this component of living cells. It is thicker than the microfilaments and thinner than the myosin filaments. The component has evolved in relation to the mechanical resistance and adhesion of cells [49]. Due to its critical role in the mechanics of cytoskeleton, the study of mechanical behaviors of IFs was focused for decades on understanding the mechanical performance of cells [7,50-53]. The mechanical significance of IFs to the living cells has already been appreciated by researchers. However, a representative mechanical model for this gel-like material still eludes us due to the difficulty encountered in obtaining their physical properties. Consequently efforts have been concentrated numerically approaches to the understanding of the mechanical contribution of IFs to cell behaviors under loading [54].

3.2 Multiscale modeling of IFs

Ackbarow et al. proposed a hierarchical multiscale model for the mechanical modeling of IFs and studied the rupture properties of their networks [25,55]. In this modeling strategy, the alpha helix was simplified by representing it as a string of virtual beads. The physical interaction between beads was obtained from mechanical testing. Figure 2 provides the schematic representation of this multiscale method while its simulation parameters are listed in Table 1 [55]. The interactions between different beads are simplified as multiple linear curves, whose stress transitions respectively sit at 5.3 Å, 11.5 Å and 13.0 Å. between 5.3 Å and 11.5 Å, strain-softening occurs after the hydrogen bond breaks after 5.3 Å. The main energy is absorbed by the flattening of the alpha helix. After 11.5 Å, strain-hardening eventuates because more energy is needed to break the peptides on the single filaments.

With assistance from this multiscale model, the mechanical properties can be quantified. Ackbarow et al. mainly analyzed the self-protective properties of IFs networks. In comparison to continuum materials, the rupture strain needed for the same flaw size on the IFs network is larger. The flaw size has negative effects on mechanical strength of IFs networks, however, the fracture toughness is better than that calculated from classical linear fracture mechanical evaluation, thereby explaining the high fracture resistance and mechanical strength of natural IFs networks in living cells.

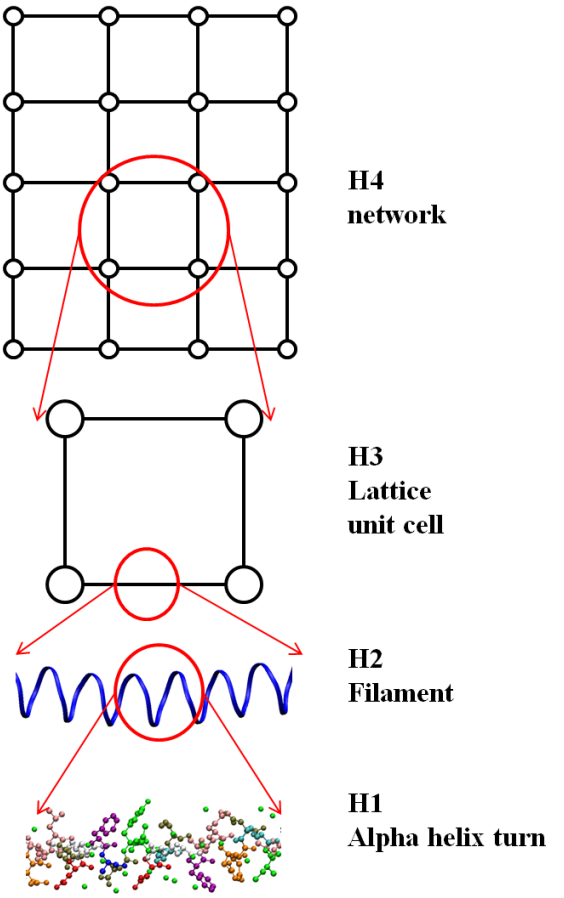

Figure 2: Multiscale model for the IFs modeling.

Table 1: Simulation parameters in the IFs multiscale modelling.

Parameters	Constants
Equilibrium distance (Å)	5.00
Stress transition points (Å)	5.3,11.5, 13.0
Stiffness (kcal/mol Å^2)	9.7, 0.56, 32.20, 54.60
Bond breaking distance (Å)	13.30
Equilibrium angle (in degree)	180
Bending stiffness (kcal/mol•rad^2)	3.44
Bead mass (amu)	400

4 Microtubules Multiscale modeling

4.1 Introduction of Microtubules

As the most rigid component of CSK, the microtubule plays an important role in the mechanical performance of living cells, such as maintaining cell morphology and adjusting subcellular structures [56-59]. Due to the mechanical significance of microtubules, enormous efforts have been devoted to studying its mechanical contribution to the physiological responses of living cells. Similar to IFs, the mechanical testing on single microtubule is difficult to be conducted, and cannot fully mimic *in vivo* environments. In order to overcome these disadvantages, multiscale numerical models of microtubules have been proposed [58-60].

4.2 Multiscale models of microtubules

In most microtubule multiscale models, tubulin dimmers are simplified as individual simulation beads. The interaction between different beads is extracted from both full atom simulation or by assumptions [26]. Figure 3 provides the physics basis of a typical microtubule model.

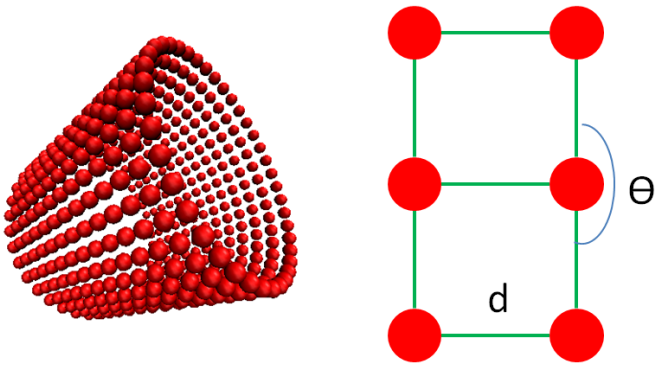

Figure 3: Coarse-grained model for microtubules.

The potential energy between simulation particles in the multiscale model can be summarized as Eq. (1). Table 2 provides the keynote parameters for Ji and Feng's model [26].

$$U = U_{long} + U_{lat} + U_{diag} + U_{b,long} U_{b,lat} + U_{d,long} + U_{d,lat} \tag{1}$$

By adopting these simulation parameters, the deformation mechanisms of microtubules under external loading have been carefully studied. This mechanical prop-

Table 2: Simulation parameters in the microtubule multiscale modelling.

Interaction	Stiffness
Longitudinal tension or compression	3 nN/nm
Lateral tension or compression	14 nN/nm
Diagonal tension or compression	3 nN/nm
Longitudinal bending	2 nN nm
Lateral bending	8.5 nN nm
Longitudinal dihedral bending	0.04 nN nm
Lateral dihedral bending	0.17 nN nm

erties study provided insights into the deformation characteristics of a whole living cell.

Based on the single microtubule modeling approaches, a long microtubule can be simplified as interconnected slender beams. By adopting beam assumption, Peter and Mofrad have developed continuum mechanics modeling of a microtubules bundle that consists of aligned microtubule filaments [59]. Their study about the mechanical deformation of microtubules bundles is deemed to explain the elongation, undulation, and delayed elasticity of axons following traumatic stretch loading.

5 Microfilament networks multiscale modeling

5.1 Introduction of microfilament networks

The microfilament network is an important CSK component that plays critical roles in many cellular processes of eukaryotic cells such as wound healing [61], cellular motility [62,63] and cytokinesis [64]. The focus of research over decades has been on the mechanisms of the force generation and transposition on the microfilament networks to understand the mechanobiology of the cellular processes in living eukaryotic cells. Continuum mechanics models have been developed for actin filaments to investigate their mechanical behavior within cell's hierarchical structure. Actin filaments were assumed to be Euler-Bernoulli beams on the continuum mechanics level in studies that were generated towards to understand the biomechanics of the microfilament networks in living cells, including strain amplification [21], force generation [22], strain-hardening [23] and structural response of randomly distributed microfilament networks [65]. However, the actin filament is a gel-like material with complex mechanical characteristics, including viscosity, strain-hardening, stress-hardening and stress-softening [66-70]. Linear continuum mechanics modeling also has the limitation in accurately characterizing the

physiological behavior of actin dynamics. These limitations call for efforts from multiscale modeling from the viewpoints of molecular simulation, in the quest to understand cellular dynamics.

5.2 Multiscale models of microfilament networks

Several multiscale models have been developed to study the mechanics of the actin filaments and microfilament networks [71,72]. Chu et al. [73] and Deriu et al [74]. independently proposed CG models for single F-actin based on the structural features of globular actin (G-actin) by thermal dynamics matching methods [73,74]. Shimada et al. introduced a serial linear spring model based on Brownian dynamics method [75]. These CG models were primarily designed to predict the dynamics behaviors of F-actin, the potential functions in these models were typical harmonic potential or Lennard-Jones (LJ) potential, which are hard to describe the nonlinear interaction between the adjacent G-actin monomers. Kim et al. [76] proposed a rod-based model to study the mechanical properties of F-actin networks based on particle modelling method. With similar modelling strategy, the rheological properties of F-actin networks have also been studied [77]. Li et al. developed a hierarchical multiscale model for the mechanics-based analysis of actin filaments [24]. In this model the interaction energy between different simulation particles is derived from all atom molecular simulations. Figure 4 provides the coarse-grained strategy of this method.

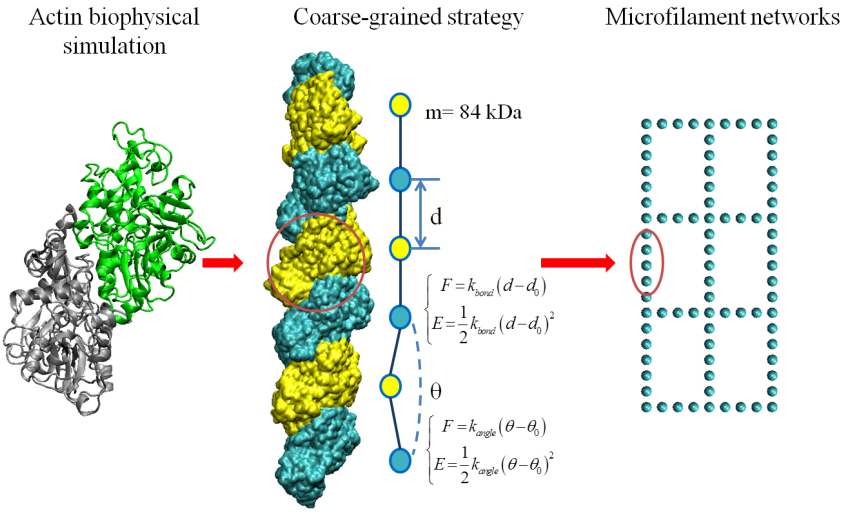

Figure 4: Multiscale modeling of microfilament networks.

The critical simulation parameters of this model are summarized in Table 3.

Table 3: Simulation parameters in the microfilament networks multiscale modelling.

Distance (Å)	Stiffness (kcal/mol·Å^2)
r1=54.00	97.53
r2=55.12	9.39
r3=55.29	13.81
r4=55.56	79.50

This multiscale bead model was validated by single F-actin tensile tests and transverse bending vibration simulation. According to the multiscale simulations of the stretching of a single layer microfilament network (4.43μm$\times 9.93\mu$m), the microfilament networks present both strain stiffening and softening in different regions of stretching. The stiffening and softening of the actin structure are not only the results of the dynamic binding of actin filament and the inducement of protein motors, but also a constitutive material behavior of single actin filaments.

6 Discussion

Development of cell mechanics has been a long and complex journey for researchers. The complex cell structures present significant difficulties that limit progresses in efforts to understand various dynamic cellular activities. Experimental techniques are limited in their capacity to capture the sub-cellular structural responses to mechanical signals at small scale level. Mechanics of CSK is critical in the study of cellular behaviors as mechanical signals are the most primary signals in nature. Modeling of CSK mechanics would provide clues for us to understand the abovementioned behaviors of living cells. Abnormal mechanical behaviors of CSK can be potential ways for the diagnosis of cellular deceases [78]. The modeling of living cells are different from the mechanics of traditional continuum material, as the microstructure of CSK undergoes continuously remodeling with respect to the complex physiological environment of living cells. Therefore, more complex modelling strategies should be explored at macroscopic level, which cover the whole spatial scale: from atoms to continuum. Multiscale simulation is the necessary tool at this stage for us to understand the underlying mechanisms of various cellular mechanics and dynamics is to be gained.

Different multiscale models for CSK modeling that have been proposed to understand the mechanical performance of important cytoskeleton components, includ-

ing IFs, microtubules and microfilaments have been gathered in their papers. With regards to the different characters of CSK components, specific modeling strategies should be adopted for its different components. These models successfully predicted some important biomechanical properties of the aforementioned components. By using these models, we are able to explain the self-protective properties of CSK. Moreover, we can track the energy flow in CSK and study the mechanical deformation correspondingly. The model can also be applied to understand many complex mechanobiological behaviors, such as muscular contraction, energy dissipation in CSK and the structural rearrangement of CSK.

However, their capacities are still far away from a full understanding of the cryptic cell mechanics. Many biophysical details are lost in the coarse-gained simulation steps. Nowadays computational power was greatly improved, but still limited in massive simulation, indicating that modelling would require efficient numerical implementation if we were to make the required further progress in this area. Take the actin filament simulation for example, the full atomic scale simulation of a 72 nm single F-actin can take up to one week of computational time to finish only 1 ns simulation on a 12 CPUs work station [79]. Both spatial and time scales cannot fully meet the requirements for us to understand the long term duration and large scale biological processes. CG method can overcome the simulation expense, but a lot of biophysical information is lost due to the simplification. Hence, more advanced multiscale models have to be developed based on advanced computational devices.

Another point about the CSK multiscale modeling is that there is no mature model to bridge these three CSK components together. In living cells, these three components coordinately work together to achieve various cellular functions. However, in the current multiscale models, this cooperation cannot be represented. A comprehensive model is needed to combine all these models together to fully understand the structural response of living cells under certain mechanical loadings. This situation suffers those methodologies such as parallel computing requires contribution as we progress further.

To sum up, multiscale modelling methods provided a powerful tool for biologists to study the mechanical responses of cytoskeleton in living cells which is significant to the understandings how living cells responses to mechanical signals. Granular modelling strategies can overcome the difficulties in non-linear physical properties prediction. However, this strategy mainly has two problems. The first problem is the computational cost. Compared to conventional modelling strategies, granular modelling strategy applied explicit governing equations to calculate the motion of modelling particles, which is more time-consuming. The computer power was greatly improved during the last 10 years and the modelling time can be extended to

a few micro-seconds from nano scale. However, biological processes can happen in a period at the timescale of hours. Hence, more powerful computational devices need to be developed to further improve the time scale of mechanobiological modelling. The second disadvantages lies in the fact that no growth factor is considered in the current models. Most studies from the granular modelling strategy are passive deformation modelling. However, it is still a great challenge to model the dynamical responses of living cells, which is initiative responses induced by the growth factors in living cells, such as the structural rearrangement of CSK. In this process, crosslinkers are dynamically forming and breaking with respects to the biological events happening in living cells. Hence, in future models, it is necessary to study the impacts from these growth factors.

7 Conclusion

Multiscale approach provides a modelling tool which can contribute to the investigation of the biomechanics of different network structures in living cells from the viewpoint of molecular simulation. With the assistance of these multiscale models, the mechanics of IFs, microtubules and microfilament networks can be better understood. These models provide insights which can contribute to the understandings of cell behaviors, and facilitate the understandings of cell degeneration related diseases and the design and manufacturing of artificial biomaterial in surgical replacement. Future development and combination of these methods are needed to systematically and accurately investigate the mechanical properties of the comprehensive cell structure response.

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